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ACUTE INFECTIVE POLYNEURITIS IN CHILDHOOD

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AMONG the conditions producing flaccid paralysis in children are poliomyelitis, muscular dystrophies, and neuritides of known and unknown origins. The latter include cases of a type which has attracted relatively little attention in childhood although frequently described in adults. These cases have been reported under a variety of names, including "acute infective polyneuritis,"[1, 2] "acute febrile polyneuritis,"[3] and "radiculoneuritis."[4, 5, 6]

During the winter of 1934-35 two patients with flaccid paralysis of this type were treated at the Union Memorial Hospital and one at the Harriet Lane Home. Recently another patient was treated at the latter hospital. A search of the Harriet Lane records disclosed three additional very similar case histories, making a total of seven cases.

CASE 1.—U. M. H., No. 42589. A. B., a white girl, aged three and one-half years, was admitted to the Union Memorial Hospital Dec. 31, 1934. The family history and past history were not contributory. Three weeks before admission the child complained of pain in the arms and legs. She was seen by a physician who is said to have found fever of 100.5° F. (rectal), nasal discharge, and an injected throat. Though she continued to complain, she remained up and about, apparently without fever. About a week or ten days before admission, however, the legs became very weak and the child took to her bed. This weakness progressed rapidly and the child became irritable.

At the time of admission the patient was completely helpless. In the lower extremities, only very slight movements of the toes and thighs were retained. The child was unable to sit up, to turn herself over in bed, or to hold up her head without support. The upper extremities were weak but less so than the lower extremities and trunk. The right arm was weaker than the left. Flexion of neck and back was extremely painful and was resisted. Deep reflexes were all lost except for feeble biceps jerks. Babinski sign and ankle clonus were absent. Abdominal reflexes were present but variable. The muscles were extremely tender. There was no impairment of the cranial nerves. Bowel and bladder control were good. No sensory loss could be demonstrated. The child complained frequently of sharp pains in the arms and legs.

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Aside from the neuromuscular findings examination revealed only a slightly injected pharynx and moderate undernutrition.

Lumbar puncture fluid, obtained on admission, showed a faint yellow tinge, Pandy four-plus, Queckenstedt negative, pressure within normal limits. There were 9 cells per cubic millimeter, 8 of them mononuclear. Later punctures showed essentially the same condition but with a gradually decreasing globulin content. The white blood cell counts varied from 12,000 to 17,000. Hemoglobin and red blood cell counts were normal. The urine was negative as were tuberculin and Wassermann reactions. Roentgenograms of the chest and long bones were negative.

For several weeks the condition seemed stationary. The temperature was normal except for occasional slight rises. Improvement began in the arms. The child was transferred to the Children's Hospital School for orthopedic care. She was discharged from that institution on July 26, 1935, completely well, and has remained well.

CASE 2.—U. M. H., No. 43410. C. S., a white boy, aged three years, was admitted to the Union Memorial Hospital on Feb. 11, 1935. The patient had had a "cold" two or three weeks before admission. He vomited once but no fever was noticed. About February 1 he fell down a flight of stairs but did not seem to be injured. For about three weeks he had had impetigo and had been treated with ammoniated mercury ointment. Six days before admission the parents noticed that the child stumbled frequently. The unsteadiness increased. There was no pain.

At the time of admission the patient could take but a few feeble steps. There was no absolute paralysis, but all the muscles of the lower extremities were about equally weak. All deep reflexes were lost except faint biceps jerks in the arms. Superficial reflexes were normal. There were no symptoms referable to the cranial nerves. No definite sensory disturbance could be demonstrated. Bowel and bladder control were not good, probably due to poor training rather than disability. There was no muscle tenderness. Impetigo was still present. Other physical findings were negative.

Cerebrospinal fluid, obtained on the day of admission, was clear and under normal pressure. It contained only three mononuclear cells per cubic millimeter, Pandy reaction was three-plus. White blood cells were 8,000 per cubic millimeter; hemoglobin, red blood cells, and blood smears were normal. X-ray films of the long bones showed no evidence of lead deposits and roentgenograms of the spine showed no sign of trauma. Nose and throat cultures were negative for diphtheria bacilli. The Schick test was negative. Later lumbar punctures showed no change in the cerebrospinal fluid except a diminution of the globulin content.

During the first ten days in the hospital the disability gradually increased until the legs were almost completely paralyzed and the trunk muscles noticeably weak. The patient no longer could stand, and, when sitting, slumped forward with a marked lumbar kyphosis. After a time the shoulder muscles lost most of their power, but the forearms and hands showed little, if any, loss of function. There was considerable muscle atrophy. The temperature curve was almost flat. A biopsy of muscle from the thigh was reported as negative.

Improvement was very slow. The patient was transferred to the Children's Hospital School where he remained until November, 1935, when he was discharged, greatly improved, but wearing special boots and an abdominal support. Three months later he had discarded these and was apparently quite well. The legs were still spindly looking but had good power. The deep reflexes were more active in the lower than in the upper extremities. There was no Babinski or other upper motor neuron sign.

CASE 3.—H. L. H., No. 90260. B. H., a white girl, aged two years, was admitted to the Harriet Lane Home Nov. 5, 1934. About ten days before admission the child

had a cold and malaise; no fever was noticed. Three days before admission weakness of the legs set in and progressed rapidly.

On admission, the legs were found to be entirely paralyzed, the trunk, arms, and neck, weak. There seemed to be some difficulty in swallowing. Sensory examinations showed hypoesthesia of the lower extremities to about midthigh. The temperature level was normal. The first lumbar puncture, on the fourth day of the paralysis, showed a clear fluid with 18 cells, 17 of them mononuclears; the Pandy test was negative. Two days later the Pandy reaction was positive and the cell count 16. The spinal fluid pressure was normal.

The hypoesthesia noted on admission disappeared rapidly and the muscles became very tender. Slight cervical rigidity developed and lasted for some time. For a few days the patient seemed dangerously ill, but slowly improved. At one stage, the deltoid muscles seemed useless when the hands and forearms had fair power. She was transferred to the Children's Hospital School on Dec. 3, 1934, and remained there eleven months, slowly recovering. A note on March 5, 1935, states that the muscles of the lower extremities were spastic, but does not mention the reflexes. This "spasticity" was temporary. It may have been the hypertonicity of muscles said to be seen sometimes during the recovery stage of a neuritis, rather than evidence of upper motor neuron damage.[4, 7] Muscle tenderness continued quite a long while. When the child was discharged from the hospital in November, 1935, she had fully recovered.

CASE 4.—H. L. H., No. 69578. M. T. B., a white girl, aged seven years, was admitted to the Harriet Lane Home on Nov. 25, 1930. The family history was not contributory. Past history was not informative except that during the summer of 1930 the child was irritable and seemed to tire easily. She suffered an attack of bronchitis accompanied by fever for a few days beginning Oct. 15, 1930. The child received four of a series of "cold vaccine" inoculations before November 1. There were no reactions to any of these. On October 30, the patient had a head cold. Two days later she complained of abdominal pain and fatigue. Her mother then noticed that the child dragged her feet in walking and had difficulty using her hands. One of her teachers had stated that in her opinion the weakness had been coming on gradually for several weeks. At least the girl became very much worse about November 1. There was no noticeable fever at that time. The child did not improve, and on November 25 was brought to Baltimore from her home in Wilmington, Delaware, and admitted to the Harriet Lane Home.

On the day of admission physical examination was essentially negative except for the neuromuscular system. The patient could sit without support but could not rise to her feet without help. All the muscles, distal and proximal, of all four extremities, were weak, some groups slightly more than others. The deep reflexes were all diminished or absent. There was no Babinski sign. No fibrillary twitchings were seen. Muscle atrophy was slight and the muscles were not tender. No sensory disturbance could be demonstrated. Sphincter control was good. There was no evidence of cranial nerve damage.

The cerebrospinal fluid was clear and under normal pressure; it contained two cells per cubic millimeter and gave a two-plus Pandy reaction. Culture was sterile. The urine was negative. White blood cells, red blood cells, and hemoglobin were normal.

There was very little objective improvement during her short stay at Harriet Lane. The child returned on Dec. 8, 1930, and again Jan. 7, 1931, for observation. She felt better but there was only slight increase in muscle power. Her physician in Wilmington, Delaware (Dr. M. Handy), reports that recovery has not been complete. There is a slight difference in the length of the two legs, and contracture of both achilles tendons. The child is able to get about and carry on all normal activities, but operative intervention is being considered because of increasing pes cavus.

CASE 5.—H. L. H., No. 56079. K. R., a white girl, aged ten years, was admitted to the Harriet Lane Home Jan. 14, 1928. Past history and family history were not contributory. On Dec. 18, 1928, the child had a toothache. Her dentist refused to extract the tooth "until the inflammation subsided." On December 24, the patient's legs were noticeably weak. This weakness increased until, a week before admission, she was unable to walk. There was no fever or headache. On the day of admission the patient was found to have weakness of all four extremities, greatest in the legs. The impairment was described as being somewhat more marked in distal than in proximal muscle groups and in flexors more than in extensors. The leg muscles were slightly tender. The cranial nerves were apparently intact. No sensory disturbance could be demonstrated. Bowel and bladder functioned normally. Deep reflexes were lost; abdominal reflexes, active. Babinski sign and ankle clonus were not present.

The cerebrospinal fluid, obtained on Jan. 14, 1928, gave a strongly positive Pandy reaction but contained only one cell per cubic millimeter. Hemoglobin, red and white blood cells were normal. Urine was negative. On February 13, the cerebrospinal fluid contained three cells per cubic millimeter and the Pandy test was less strongly positive (two-plus). Spinal fluid Wassermann was negative. Tuberculin test was negative (0.1 mg.).

Within a few weeks the patient was greatly improved. Tonsillectomy and adenoidectomy were performed. When last seen in the dispensary, May 8, 1928, the child was quite well. All the reflexes were normal and there was no muscular weakness or atrophy.

CASE 6.—H. L. H., No. 69611. J. C., a Negro girl, aged ten years, was admitted to the Harriet Lane Home on Dec. 1, 1930. Past history and family history were not informative. The story of the present illness, as obtained from the patient's grandmother, was not clear. It was stated that the child had tonsillitis for a few days in February, 1930. During that illness a brother is said to have remarked that the patient did not walk well. However, she was able to return to school and play without difficulty. In the spring of that year the child had pain and swelling in the right knee, later in the left knee also. She still managed to get about as usual. The grandmother was away during July and August, but did not think there had been any illness during that period. Almost two months before coming to the hospital it was noticed for the first time that the child could not raise her arms above the shoulders and could not get up from a supine position without first rolling over on her abdomen. There were no pains, fever, headaches, or convulsions. Speech, swallowing, and bowel and bladder control were normal.

It is difficult to be sure whether the true onset of this child's illness was in February or late September. The latter seems more probable. Perhaps the joint pains in the spring were due to a low-grade rheumatic fever.

At the time of admission, Dec. 1, 1930, the patient was found to be undernourished and poorly developed. She had dental caries and large tonsils. The heart, lungs, and abdomen were negative. The muscles generally were slender but not definitely atrophic. There was no pseudohypertrophy of muscle. The muscles of the hips and thighs were weak, those below the knees fairly strong. There was a marked lordosis when standing and the gait was waddling. In the upper extremities, too, all muscles were weak but the proximal groups more so than the distal. The neck was also involved, the child being unable to hold her head up steadily. The tendon reflexes were all present, but diminished. The knee jerks were less active than the ankle jerks. Observers differed in opinion as to whether or not there was a Babinski sign.

Cerebrospinal fluid, obtained by lumbar puncture on Dec. 2, 1930, was clear, under normal pressure, contained 5 cells and gave a negative Pandy reaction. The

white blood cell count was 9,600 per cubic millimeter; differential, normal. The red blood cells were normal in appearance and the count 4,970,000 per cubic millimeter. Hemoglobin was 100 per cent (Sahli). The urine was clear, yellow, acid; specific gravity, 1.017; albumin, 0; sugar, 0. Microscopic examination showed an occasional white blood cell and granular cast. Wassermann and tuberculin tests were negative.

The patient remained in the hospital for twenty-three days. At first she became a little worse and it was noticed that her face, while not paralyzed, appeared to be "ironed out." She was discharged, unimproved, with a tentative diagnosis of muscular dystrophy. When she returned to the dispensary a month later very much improved the impression was changed to polyneuritis.

On Jan. 28, 1931, the child was found to have mumps. On Dec. 8, 1931, she returned with pneumonia at the base of the right lung. In the interval she had attended school and was getting along well. At this time, in addition to her pneumonia, she showed generalized weakness, out of proportion to her acute illness. There was no noticeable weakness of any particular muscle groups. Her fever lasted only a few days, but the pulmonary consolidation cleared very slowly. Electrical stimulation showed a reaction of degeneration. When the patient was able to get up, she did so by "climbing her legs" similar to a patient with pseudohypertrophic muscular dystrophy. The child regained her strength partially and left the hospital Jan. 17, 1932. At home, she improved considerably but continued to rise by "climbing her legs." On May 12 a tonsillectomy was attempted but was stopped because of cardiac and respiratory failure. Two days later the tonsils and adenoids were removed without difficulty and the child recovered uneventfully. A month later she contracted a "cold," lost weight, and seemed weaker. On July 7 she returned to the dispensary feeling better. All the reflexes were normal and she seemed stronger. The child died at home on Aug. 7, 1932, after an acute illness of four days' duration. She was seen on the second day of her final illness by a private physician who made a diagnosis of myocarditis.

Because this child was examined by several different physicians on her various visits to the hospital and dispensary, and not followed throughout by any one observer, it is difficult to evaluate the improvement and relapses recorded. Such a course was not observed in any of the other cases, nor is that characteristic of the cases of acute infective polyneuritis reported in the literature. The distribution of the lesions in this case is, however, very characteristic; especially the involvement of the face and proximal muscle groups in the extremities.

CASE 7.—H. L. H., No. 67406. M. G., a Negro girl, aged eight years, was admitted to the Harriet Lane Home on March 1, 1937. She is the eighth of twelve children in a family of poor economic status. The child has been brought to the Harriet Lane out-patient department from time to time for several years and was known to have mediastinal tuberculosis. The dietary history is very unreliable. The family eat well when the father has work and poorly when he has none. Recently they have been living mainly on beans, cabbage, and potatoes, with almost no meat, eggs, or milk.

On Feb. 26, 1937, the mother thought that the patient looked thinner than usual. She called the child who collapsed and fell as she started toward her mother. The patient was unable to stand and had to be carried to her bed. The child complained of pains in her arms and legs and cried when she was touched anywhere. She would not eat. No fever was noted. The patient was brought to the hospital on the fourth day of her illness.

At the time of admission the child's temperature was 98.6° F. (rectal); pulse, 86; respiration, 16; weight, 18.5 kilograms. Positive physical findings included malnutrition, moderately rachitic chest, localized apical systolic murmur, and slight diastasis recti in addition to the neuromuscular changes. There was tenderness to

light pressure all over the body and generalized weakness of extreme degree. The patient was unable to stand or walk and could hardly maintain a sitting posture. There was no very great difference in power between various muscle groups but the muscles of the neck, shoulder, and pelvic girdles seemed a little weaker than the distal muscle groups of the extremities. The face was rather expressionless but not paralyzed and there was no other demonstrable cranial nerve lesion. The deep reflexes were all lost. Abdominal reflexes were active; there was no Babinski sign.

Hemoglobin was 98 per cent; red blood cells numbered 5,450,000; white blood cells, 7,140; polymorphonuclear neutrophiles, 46 per cent; immature neutrophiles, 5 per cent; eosinophiles, 5 per cent; lymphocytes, 45 per cent. The urine was negative.

Spinal fluid on March 1 was clear; Pandy, two-plus; cells, 2; sugar, present qualitatively. On March 4, the spinal fluid was clear; Pandy, three-plus; cells, 0; sugar, 72 mg. per cent. On March 11, the spinal fluid was clear; Pandy, four-plus; cells, 0. Blood lead (spectroscopically determined) was 0.056 mg./100 c.c. (high normal); spinal fluid lead, 0.

X-ray films of the long bones showed no "lead lines." X-ray films of the chest showed old mediastinal tuberculosis with calcification. Skin tests for trichiniasis were negative. Wassermann reaction was negative.

Recovery began in about two weeks. The patient was discharged on April 6, 1937, almost entirely well. When she returned for examination on April 19 recovery was apparently complete.

DISCUSSION

These seven patients had extensive paralysis or paresis of lower motor neuron type. For the most part there was profound weakness, rather than complete paralysis. The involvement was widespread and symmetrical, not spotty. In Case 2 the shoulder, and in Case 6 the shoulder and pelvic girdle muscles were strikingly weaker than the more distal groups, so much so that the Werdnig Hoffman type of spinal muscular atrophy was suggested. In Cases 3 and 7 also proximal muscle groups were more affected than distal but the difference was not so great. Only in Case 5 was the impairment described as more marked distally, and more in flexors than extensors. In no case was wrist-drop or ankle-drop a prominent feature. Patients 1, 3, and 7 had severe pain and muscle tenderness; Patient 5 had milder muscle tenderness; the others were free of pain. Cranial nerve involvement occurred in Case 3, in which there was difficulty in swallowing, and Case 6, in which there was slight facial weakness. Some degree of facial diplegia has been reported in a large percentage of the cases of acute infective polyneuritis in adults. Perhaps it is more difficult to detect slight symmetrical facial weaknesses in the smooth faces of children than in the more lined faces of adults. Except for tenderness and pain, the only sensory disturbance was the fleeting hypoesthesia of the lower extremities in Case 3.

Six of the seven patients had spinal fluid containing increased globulin but few cells (maximum 18). In the other case lumbar puncture was not done for at least two months after the onset of paralysis. In Case 3 globulin was absent from the first spinal fluid obtained but present two days later.

Four of these children had respiratory infections within a week or two of the onset of paralysis. One case followed an abscessed tooth. The former association has been reported frequently in adult cases and Barker[8] has reported the latter once. One cannot be sure that these seemingly mild antecedent illnesses were responsible for or related to the paralyses.

The onset, in each of the cases described, was in autumn or winter. In so small a group, however, this seasonal incidence is probably not significant.

Poliomyelitis was considered as a possible diagnosis in these cases, although none of them occurred during an epidemic of that disease. The minimal fever and the marked symmetry of the lesions were against that diagnosis. In individual cases there were other objections such as the slow spread of the paralysis in Case 2 and the temporary sensory loss in Case 3. In several instances lumbar punctures were done too long after the onset to have found increased cells in the spinal fluid even if the disease was poliomyelitis. On the other hand, in Case 2, in which lumbar punctures were done during the spread of the paralysis, and in Cases 3 and 7 in which they were done early, the spinal fluid cell counts were low. The highest count in the whole series was eighteen cells per cubic millimeter. In poliomyelitis the spinal fluid globulin is rarely so abundant as it was in Cases 1 and 7. Case 4 was more like infantile paralysis than the others in that contractures developed. They are relatively mild when compared to the extent of the original paralysis.

So far as it was possible to ascertain, none of these patients had diphtheria. That disease is uncommon in Baltimore but there are a few cases each year. Nose and throat cultures for diphtheria organisms were negative in these cases.

Each patient was investigated for lead poisoning by history, x-ray of the long bones, and examination of the red blood cells for stippling. In three cases the blood was examined spectroscopically for lead. The results were all normal.

There was no history of exposure of any of these patients to other neurotropic toxins such as alcohol or arsenic. The diets did not suggest vitamin B deficiency. The skin changes, photophobia and sweating, associated with acrodynia, were absent.

The cases described above are appreciably similar to those described by Landry in his "Note sur paralysie acendante aigue," published in 1859. Landry reported ten cases, five of his own and five gathered from the literature. Of the ten patients, two died, one of Landry's patients and one of Olivier's, first reported by the latter in 1837. A translation of Landry's description of his fatal case may be found in Viets' article,[9] "History of Peripheral Neuritis as a Clinical Entity." The patient, a man, lived eight days after the onset of his paralysis which was ascend-

ing and practically symmetrical, involving trunk and neck as well as extremities. The muscles were nowhere completely paralyzed. Weakness was greater in the lower than in the upper extremities. The shoulder girdle muscles were the most affected groups in the upper extremities; elsewhere the weakness was somewhat more marked distally. The patient died apparently of respiratory failure. Postmortem examination in this and Olivier's case did not reveal any seemingly significant abnormalities in the central nervous system. The peripheral nerves were not examined. The other eight patients all recovered completely, improvement taking place in reverse order of development.

In 1859, the occurrence of paralysis as the result of disease of peripheral nerves had been the subject of speculation but had not been generally accepted, nor was degeneration of the peripheral nerves established pathologically for several more years. In the next few decades many types of neuritis of known and unknown etiology were described, including "polyneuritis with facial diplegia" (Pierson, 1869) and "acute febrile polyneuritis." The latter was included in the early editions of Osler's Modern Medicine. Meanwhile the term "Landry's paralysis" has been loosely applied to ascending paralysis of all sorts, including myelitis and poliomyelitis as well as polyneuritis.[10] One can find four or five very different definitions of the term in as many standard textbooks. Most authors agree in describing "Landry's paralysis" as hyperacute and highly fatal, despite the full recovery of four out of five of Landry's own patients. Perhaps it will not add too greatly to the confusion to point out that there is a striking similarity, clinically, between Landry's cases and many of those since described as acute infective polyneuritis or radiculoneuritis.

During the World War cases of the latter type attracted considerable attention. In 1917 Guillain, Barré, and Strohl[4] reported two cases of ascending flaccid paralysis with marked increase in spinal fluid globulin but no pleocytosis. Both patients recovered. One of them had temporary hypertonicity of the leg muscles while recovering, but no hyperactive reflexes or other upper motor neuron sign. The authors considered this compatible with a neuritis. They regarded the illness as a "radiculoneuritis" and called the spinal fluid findings "albumino-cytologic-dissociation." Some French authors now call the combination the "Guillain-Barré syndrome." In 1925 Guillain, Alajouanine, and Perisson[5] reported two additional cases.

In 1917 Gordon Holmes[3] reported briefly twelve cases of what he called "acute febrile polyneuritis." The subjects had slight fever, extensive flaccid paralysis and variable sensory disturbances. The paralysis was more marked distally. Bowel and bladder disturbances of mild degree occurred in several cases. Two patients died. At autopsy peripheral neuritis was found.

About a year later Bradford, Bashford, and Wilson[1] made a comprehensive study of thirty cases with eight deaths—also occurring in the British army. They used the title "acute infective polyneuritis" and thought they were dealing with the same disease reported by Gordon Holmes in spite of some differences in symptomatology and pathologic findings. A number of the patients gave a history of a short illness with slight fever from a few days to a few weeks before the onset of paralysis. The paralysis involved the muscles of the extremities equally or in some cases the proximal muscles more than distal ones. Facial weakness, often difficult to detect, was present in most instances. Mild, transitory sphincter disturbances occurred in a few cases. Sensory findings were quite variable; usually some slight disturbance was present. Except when death occurred early in the disease from respiratory failure or pneumonia the patients recovered completely, often requiring many months of convalescence. In cases in which autopsy was done widely disseminated lesions were found. The peripheral nerves showed both degenerative changes and interstitial inflammatory reaction. In the posterior root ganglia there were degenerative changes in the ganglion cells and some increase in small round cells. The gray matter of the cord was hyperemic and the neurons, especially in the anterior horn cells, showed degenerative changes. Punctate hemorrhages were seen in the gray matter of the cord and small round cells were increased in number. There was no perivascular round cell infiltration as seen in poliomyelitis. The Betz cells of the cortex showed slight evidence of degeneration. The meninges, described in only one case, showed marked congestion. These authors claimed to have reproduced the disease in monkeys by subdural inoculation of glycerinated spinal cord from three of the fatal cases. They also claimed to have isolated a filtrable organism capable of inducing the disease, but retracted this claim following criticism of their work by Arkwright.[11]

Foster Kennedy[12] reported on some of the same cases included in Bradford, Bashford, and Wilson's study. Because of the widespread lesions he suggested the name "infective neuronitis" instead of polyneuritis.

Casamajor[13] published a report of a few cases belonging to this group with two autopsies. His pathologic findings differed somewhat from Bashford's. Casamajor stressed the involvement of the meninges and the anterior and posterior spinal roots within the dura. He found less extensive degenerative changes in the gray matter of the cord than Bashford reported and thought that some of the latter's findings were the result of postmortem changes.

Very few lumbar punctures were done in this entire series of British army cases. Those reported were negative.

Since the war period collections of cases of ascending flaccid paralysis have been reported by a number of different writers under several

names. In 1925 Bériel and Dévic[14] reported a group as "Peripheral Forms of Epidemic Encephalitis." Others in France, Germany, and America have tried to establish a relationship between epidemic encephalitis and this type of paralysis. Series of cases with facial nerve involvement have been reported as polyneuritis with facial diplegia.[15] In France "radiculoneuritis" and in Germany "acute primary polyneuritis"[16] are terms widely used. In 1934 Debré, Marie, and Messimy[17] reported one case in a boy of five, whose weakness was most marked in the pelvic girdle musculature. They called the condition "pseudomyopathic polyneuritis." Quite recently Guillain[6] has reviewed the subject and brought his own series of cases up to ten in number. Guillain places great stress on the spinal fluid findings, and believes that his cases, which were relatively mild, differ in etiology from the more severe type such as Bradford, Bashford, and Wilson's group. One of the few reports devoted to this condition in childhood is that of Mettel,[2] published in 1924.

In most of the recent cases the spinal fluid findings have been those described by Guillain and his coauthors. The globulin content has often been extremely high; even the Froin syndrome has been reported. When electrical reactions have been tried, usually qualitative changes have been found but seldom a complete reaction of degeneration. The facial nerves have been involved in a large proportion of the cases and occasionally lower cranial nerves, but lesions of the nerves above the seventh are rare. The distribution of the paralysis has usually been as described by Bradford, Bashford, and Wilson, that is, involving practically the entire somatic musculature with a tendency to affect proximal muscles of the extremities more severely than distal ones. Often the course has been definitely ascending, but in some cases, otherwise indistinguishable, the upper extremities have been involved simultaneously with the lower. Sensory phenomena have been variable, usually absent or very mild, seldom forming a prominent part of the picture. In some cases, fever, usually of moderate degree, has been present during a brief illness preceding the paralysis, but the onset and course has been almost or entirely afebrile in nearly all.

Because the great majority of patients have recovered, pathologic data are not abundant. In those patients who have been studied at autopsy the lesions have been most marked in the spinal roots and peripheral nerves, but slighter changes have often been present in the meninges, spinal root ganglia, and cord and occasionally slight degenerative changes in cortical cells. The validity of some of the latter findings has been questioned. In the peripheral nerves Dechaume[18] found the myelin sheaths and Schwann cells to be more severely damaged than the axis cylinder proper. Evidences of both toxic degeneration and inflammation have been found, the former predominating.

Except for Bradford, Bashford, and Wilson's afterward retracted statement, there have been no claims to the establishment of a specific etiologic agent for this disease. There has been considerable speculation on the possibility of the virus of epidemic encephalitis or some unknown neurotropic virus being the culprit. Some investigators believe that the damage is probably done by a toxin without direct invasion of the nervous system by living organisms. It has been suggested that the noxious agent, virus, or toxin, must be propagated along and widely disseminated over nerve pathways.[19] Nicolau[20] coined the term "septineuritis" to express this.

One is probably not justified in presenting "acute infective polyneuritis" as an established disease entity. The etiology is unknown, the pathologic anatomy has not been well worked out and there is no absolutely pathognomonic clinical sign. Nevertheless, the symptom complex as described recurs frequently enough, and is distinctive enough to make it convenient to group together cases of this type and to give them a name. Whether the syndrome can be produced by a number of agents or only one remains to be seen.

The name "acute infective polyneuritis" was first used by Bradford, Bashford, and Wilson. It has been used in the title of this paper because it is the title most frequently encountered in the English literature. It is not a good term because the disease has not yet been proved to be of infectious origin and because pathologically there is more than a peripheral neuritis. "Acute febrile polyneuritis," which from the standpoint of priority is the term to use, is objectionable because fever plays so inconspicuous a part in these cases. In the French literature "radiculoneuritis" is most often encountered.

SUMMARY AND CONCLUSIONS

1. Seven cases of extensive ascending flaccid paralysis in young children have been described. These cases are thought to belong to a group described in the literature under a number of names, prominent among which are "acute infective polyneuritis" and "radiculoneuritis."
2. This group is characterized by:
   a. Widespread, frequently ascending, flaccid paralysis or paresis tending to affect proximal muscles in the extremities as much as or more than distal ones. The involvement is symmetrical and widespread, not patchy.
   b. Frequent facial nerve involvement—sometimes the lower cranial nerves, but not the higher ones.
   c. Sensory disturbances may be present or absent. They are variable and always less prominent than the motor phenomena. Muscle tenderness occurs frequently.

d. Bowel and bladder disturbances are present in some cases, but are relatively mild and transient.

e. The spinal fluid usually shows increased globulin with little or no increase in cells.

f. Fever is mild or absent.

g. There is often a history of a mild illness, usually respiratory, preceding the onset of paralysis.

h. Unless death occurs early in the disease from respiratory failure, recovery usually takes place without permanent paralysis.

3. Not enough pathologic data have been accumulated to establish a firm anatomic foundation for this disease. In those cases which have come to autopsy the spinal roots and peripheral nerves have borne the brunt of the attack, but lesions have also been described in the meninges, posterior root ganglia, gray matter of the cord, and even the cerebral cortex. The descriptions of the lesions by various observers differ considerably.

4. Until more information can be obtained it is better to regard acute infective polyneuritis as a syndrome, possibly of multiple origin, rather than a proved disease entity.

5. There is no specific treatment. Appropriate orthopedic care is important for the prevention of contractures.

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DURAL SINUS THROMBOSIS IN EARLY LIFE

I. The Clinical Manifestations and Extent of Brain Injury in Acute Sinus Thrombosis

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THIS study is concerned with the clinical and pathologic findings in 80 instances of thrombosis of the dural venous sinuses in infants and children. Only 3 patients were over three years of age (1 was six; one eight; and a third, eleven and one-half years). A report of 50 of these patients has been made previously.[1] These cases have been divided into two groups. The first is composed of 77 patients in whom either the clinical history or the pathologic findings indicated sinus thrombosis of less than one month's duration. The second group is composed of 3 patients who survived the acute thrombosis and died later. This arbitrary grouping is merely to facilitate description; it is clear that there is no precise temporal or pathologic demarcation between the two groups.

The present paper deals with those 77 patients who had antemortem, either unorganized or incompletely organized thrombi in the dural venous sinuses. Our purpose is to correlate the extent of brain injury with the localization of the thrombi in the venous sinuses and their tributary veins. Especial attention is given to the large group of infants and children in whom the thrombosis could not be attributed to the localization of a demonstrable infectious agent in the sinus wall or tributary veins.

SINUS THROMBOSIS ASSOCIATED WITH SEPSIS

The classic descriptions of thrombosis of the dural sinuses deal almost wholly with those instances which result from infections spreading to the sinuses from adjacent foci, such as the mastoid, upper lip, or orbit. In the present series, however, the sinus thrombosis could be attributed to recognizable septic processes in only 42 patients (52 per cent). The original lesions were otitis media, mastoiditis, cellulitis of the scalp, and bacteremia without meningeal localization.

In 7 patients, lateral sinus thrombosis resulted from inflammation in the middle ear and mastoid region (8.7 per cent). This low percentage undoubtedly is due to the fact that many patients with thrombi of this type in the lateral sinuses subsequently recover.[2] Many extensive descriptions of the complications of otitis media including lateral sinus thrombosis with or without mastoiditis have been made and the present material has uncovered no new facts relating to them. In the patients of the series, there was extension of the thrombus from the lateral sinus

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into the straight sinus in one instance and into the superior longitudinal sinus in two instances. In view of the cerebral softening and hemorrhage present in the two cases in which the superior longitudinal sinus was involved and the absence of cerebral lesions when the thrombi were confined to the lateral sinuses, it might be assumed that extension into the longitudinal sinus is a serious complication.

There were 22 instances of sinus thrombosis associated with meningitis (27.5 per cent of the total series). In all of these patients it was impossible to segregate the clinical manifestations due to the thrombosis from those resulting from the meningitis. The various etiologic agents were as follows:

Bacillus influenzae 10; pneumococcus 7; *Bacillus acidi lactici* 1; *Bacillus tuberculosis* 1; *Bacillus coli* 2; Unidentified 1.

A thrombus was found in the superior longitudinal sinus in 20 patients. It was confined to the right sigmoid sinus in one patient and to the right lateral sinus in another. A thrombus in the superior longitudinal sinus frequently was accompanied by thrombi in other dural sinuses and cerebral veins (13 cases). The amount of cerebral damage resulting from the occlusion of venous channels was difficult to determine exactly, owing to the presence of the meningitis. However, in the 20 instances in which the superior longitudinal sinus was thrombosed, there were intracerebral hemorrhages and necroses or subarachnoid hemorrhages. In view of the infrequency of such findings in uncomplicated meningitis, their occurrence may be attributed in large part to occlusion of the venous sinuses and their tributary veins. The hemorrhages and necroses can alter but little the progression of those forms of meningitis which are almost invariably fatal without such complications. On the other hand, certain infections of the meninges, especially those due to the meningococcus and *Bacillus influenzae*, have been treated successfully in a certain proportion of cases with specific antiserums. It is recognized that permanent impairment of cerebral function often follows recovery. Frequently at a later date such patients are studied at necropsy without discovery of any clear explanation for the cerebral injury. In such cases, we wish to urge the study of the venous sinuses, especially the superior longitudinal sinus in order to identify organized thrombi, even though they result in only partial occlusion.

In the series, there were 7 cases (8.7 per cent) resulting from cellulitis of the scalp. Four were due to *Staphylococcus aureus*, two to *Streptococcus hemolyticus* and one to pneumococcus. In these patients the infection seemed to spread by way of emissary veins in the scalp which communicated freely with the dural venous sinuses. The thrombi were located as follows: superior longitudinal sinus 3; cerebral veins 1; lateral sinus 7.

In two of the patients with involvement of the superior longitudinal sinus there were subarachnoid and cortical hemorrhages while in one

patient the subcortical tissues were also involved. In the third patient with involvement of this sinus the process was located in the terminal portion and was very recent though definitely antemortem. There was no cerebral injury. The four patients, in whom thrombi were found only in the lateral sinuses, presented no hemorrhages or necroses in the brain. A variable amount of vascular congestion was found in all cases. There was definite cerebral edema in four instances.

The remaining six cases of thrombosis with a possible infectious origin were associated with bacteremia. There was no microscopic evidence of localization of the infectious agent in the central nervous system. In these patients, the following organisms were isolated from the blood in the heart at necropsy: *Streptococcus hemolyticus* 2; *Bacillus paratyphosus B* 2; *Bacillus pyocyaneus* 1; *Bacillus coli* 1.

The thrombi were located as follows: superior longitudinal sinus 4; cerebral veins 5; lateral sinus 6; straight sinus 4; vein of Galen 3.

At least one of these patients might be included with those not associated with demonstrable infection. This patient was a female infant, eighteen months of age. Two weeks after the onset of a rather mild infection with *Bacillus paratyphosus B*, the clinical evidences of the infection had disappeared almost entirely. Suddenly she developed evidence of severe meningeal irritation with a fever of 109° F. She died on the following day. At necropsy unorganized thrombi were found in the posterior three-fourths of the superior longitudinal sinus, the lateral sinuses, the straight sinus, and the great vein of Galen. There were small necroses and hemorrhages in the cerebrum and meninges. Culture of the blood in the heart showed only *Bacillus coli*. *Bacillus paratyphosus B* was obtained, however, from the bone marrow and from the meninges, though there was no histologic evidence of meningitis.

Two of the three remaining patients of this group in whom thrombi were found in the superior longitudinal sinus presented early lesions without cerebral injury. The third showed subarachnoid and intracerebral hemorrhages with cortical and subcortical necroses.

SINUS THROMBOSIS ASSOCIATED WITH SURGICAL PROCEDURES

There were four patients in the series in whom sinus thrombosis developed after surgical procedures. No evidence of infection was found in any of the cases. The history of the following patient serves as an example of thrombosis following intracranial surgery:

The patient was a male infant, two months of age. From the time of his birth he had had a hydrocephalus which was progressing rapidly. Coagulation of the right choroid plexus was performed. After operation, the patient developed signs of shock and hyperthermia. Death occurred on the fifth postoperative day. At necropsy a firm laminated thrombus was found in the superior longitudinal sinus. There were areas of softening and hemorrhage in the right parietal lobe and each

thalamus. It was impossible to state how much of the injury was due to the thrombosis and how much to spreading of the coagulating current.

Sinus thrombosis as a sequela of surgery is unusual. The number of cases in this group is small when compared with the large number of operations performed at The Boston Children's Hospital during this time (1926-1936). It is also apparent that this group forms a small percentage of the total number of instances of sinus thrombosis. Evans[3] has reported two interesting instances of postoperative thrombosis of the superior longitudinal sinus, one after herniotomy and the other after operation for hypertrophic pyloric stenosis.

SINUS THROMBOSIS UNASSOCIATED WITH SEPSIS OR SURGICAL PROCEDURES

There is a large group of infants and children in which thrombosis of the dural sinuses occurs in the absence of bacteremia, demonstrable localization of bacteria in the central nervous system, regional spread of an infectious process directly into the sinuses, or trauma. In the present series, this group was composed of 33 patients (41.2 per cent). Of these, 31 patients died within one month after the probable time of formation of the thrombus. These have been designated as instances of acute sinus thrombosis. The other two patients survived the initial illness and cerebral damage consequent to the thrombosis, only to succumb at a later date. Because of the many unusual features presented by these two patients, they will be considered in a separate report. The instances of acute thrombosis will be analyzed in the following pages. It becomes apparent in studying the series that such an arbitrary division into "acute" and "chronic" or "healed" sinus thrombosis is merely a matter of convenience in description since they differ clinically only in length of course and pathologically only in degree of repair of lesions.

CLINICAL MANIFESTATIONS

The clinical manifestations of the patients were extremely varied. There were certain features in common, however, which aid in the understanding of the pathogenesis of the process and also possibly in clinical diagnosis. All the patients were less than thirty months of age (average age, nine months) indicating that the disorder is rather sharply limited to the period of life during which the anterior fontanelle is open and nutritional disturbances are most frequent and severe.

Analysis of the histories of the patients in this group reveals, as a rule, a severe nutritional disturbance. This disturbance developed either in previously well-nourished infants, or less frequently in infants with various types of chronic disease. A composite history would be somewhat as follows:

A previously healthy infant of either sex suddenly developed symptoms of gastrointestinal disturbance. This was characterized by persistent and severe diarrhea, with 8 or more liquid bowel movements a

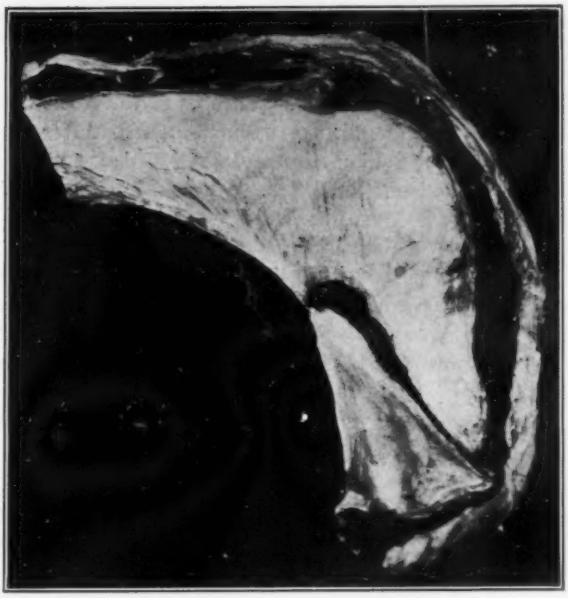

Fig. 1.—Photograph of the falx and tentorium showing the superior longitudinal, lateral, and straight sinuses completely occluded by thrombi. Thrombi from the vein of Galen are also attached to the specimen.

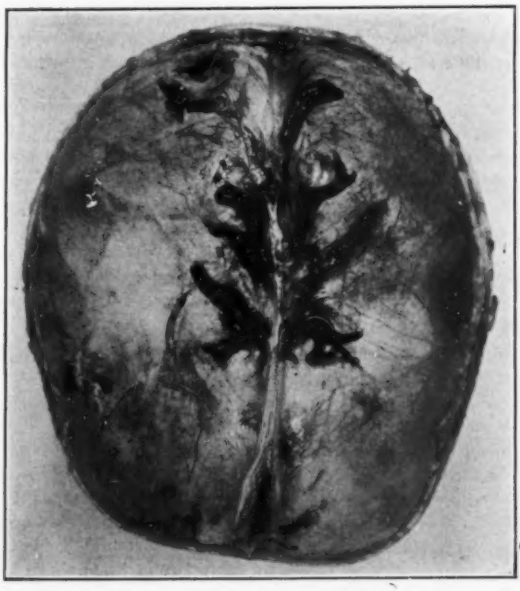

Fig. 2.—The calvarium from a patient with thrombosis of the superior longitudinal sinus. Note the numerous tributary veins which are distended with thrombi.

day. Vomiting occurred occasionally after feeding. The temperature showed wide swings from subnormal to 105° F., but most of the time was about 103° F. Physical examination revealed marked prostration and evidence of severe dehydration. Cultures of the stools disclosed no enteric pathogens. Blood cultures were negative. After two to five days, convulsions of Jacksonian character developed; the neck was rigid, and the tendon reflexes were reduced. There was a period of extreme hyperthermia, followed by death. Postmortem examination revealed extensive thrombosis of the dural sinuses with maximal and oldest involvement in the superior longitudinal sinus, associated with subarachnoid hemorrhage and intracerebral necroses and hemorrhages.

All these features are not always exhibited by a given patient. There were certain variations of the picture to which special attention should be called. In several patients, no neurologic symptoms were detectable. The clinical manifestations were those of very severe gastrointestinal disturbance with fatality in a few hours or days after the onset of symptoms. An example of this type is the following:

CASE 1.—J. H. was a two months premature, white, male infant, four weeks of age. At nine days of age the patient weighed 5½ lb. and at twenty-four days, 5 lb. Three days before admission to the hospital the infant became irritable and refused to nurse. Each day he passed five or six loose stools. The temperature was 103° F. The fever and diarrhea persisted. On the second day after onset of symptoms he was admitted to the hospital because of severe vomiting. The temperature at this time was 103.6° F. Physical examination showed a critically ill, apathetic infant. Respirations were shallow. He was cyanotic and there was evidence of dehydration. The patient was breathing shallowly; the cardiac rate was 55 per minute. Seventy cubic centimeters of 10 per cent glucose were given intravenously. Because the history and physical findings revealed nothing to account for the critical condition of the patient, a diagnostic lumbar puncture was done. The pressure of the spinal fluid was 280 mm. of water. The spinal fluid was deeply xanthochromic. The test for globulin was strongly positive; the sugar content was normal. On microscopic examination there were 6,000 red blood cells (many of which were crenated) and 6 white blood cells per cu. mm. Spinal fluid and blood cultures were negative. There were no convulsions or other clinical manifestations of involvement of the central nervous system. The patient died five hours after admission. The clinical diagnoses were prematurity, undernutrition, and overwhelming sepsis.

The postmortem examination disclosed an acute ulcerative colitis, dural sinus thrombosis and extensive alterations in the brain. The cultures of the blood of the heart showed no growth and no pathogens were isolated from the intestine. There was a thrombus filling the entire superior longitudinal sinus and extending into its tributary cerebral veins, the lateral sinuses, the straight sinus and the great vein of Galen. The convolutions were flattened. There was an area (3 by 3.5 cm.) of recent subarachnoid hemorrhage over the posterosuperior portion of the left frontal lobe and a similar area (3.5 by 1.5 cm.) over the right frontal lobe. Beneath each hemorrhage, there was a zone of cerebral softening which averaged 1 cm. in depth. A large area (8 by 2.5 cm.) of periventricular softening and hemorrhage, for the most part above the ventricle, was found in the left cerebral hemisphere (Fig. 5). A similar though somewhat larger area of necrosis and hemorrhage was present in the right cerebral hemosphere. No intraventricular hemorrhage was found, though the ventricular walls were necrotic. Around the intracerebral tributaries of the

thrombosed, distended superior cerebral veins there were areas of hemorrhage and softening. There were no lesions of the pons, medulla, or cerebellum.

Microscopic studies showed very early fibroblastic invasion in the thrombi in the dural sinuses. The areas of cerebral damage were characterized by recent necrosis of tissue and hemorrhage. There was no evidenec that the process was more than a few days in duration. There was no proliferation of astrocytes.

It is difficult to correlate the clinical and pathologic findings in such a patient. No definite signs referable to the central nervous system could be elicited. There is little clinically to differentiate these patients from those in the large group who die of acute nutritional disturbance with very meager gross and microscopic lesions. Examination of the cerebrospinal fluid is a very useful diagnostic procedure in establishing the presence or absence of sinus thrombosis.

In most of the patients, however, after a period of from three days to two weeks, symptoms referable directly to the central nervous system become apparent. As a rule these are sudden in onset and are followed by a very stormy clinical course. The neurologic manifestations within certain limits are dependent upon the regions of the brain involved and upon the extent of cerebral injury. They are characterized therefore, by their diversity, which contributes much to the confusion surrounding the clinical diagnosis of dural sinus thrombosis.

The most constant neurologic signs are those referable to irritation of the meninges. These are stiffness of the neck and positive Kernig's and Brudzinski's signs. Photophobia, however, occurs rarely. The most conspicuous neurologic findings, on the other hand, are related generally to intracerebral hemorrhage and necrosis. Among these, extreme elevation of temperature is common. Many of the patients had temperatures as high as 106° F. and even 109° F. Dural sinus thrombosis may be listed as one of the important causes of very high fever in early life. The fever may be attributed to interference with the central control of temperature regulation. In the patients having the highest temperatures, there were such extensive necroses and hemorrhages in the cerebral hemispheres that it was impossible to designate any single lesion as the one responsible for hyperthermia. Convulsions, generalized or Jacksonian in character, were very frequent. Inasmuch as generalized convulsive seizures are common in various diseases of infancy in the absence of demonstrable cerebral lesions, the difficulties in differential diagnosis on the basis of these manifestations alone are apparent. However, in many instances the convulsions were Jacksonian in character. This serves as an important point in the recognition of sinus thrombosis. Convulsions beginning in the hand, arm, or leg, which later become generalized, have in the patients of this series a definite anatomicophysiologic explanation. Patients developing Jacksonian attacks in the course of sinus thrombosis all had thrombi in the superior longitudinal sinus with extension into the superior cerebral veins, chiefly those draining the

middle third of the lateral aspect of the cerebral hemisphere. There were foci of cortical and subcortical necrosis and hemorrhage accompanying these venous thrombi.

Other neurologic disturbances include interference with extraocular movements and positive Babinski sign. Nystagmus and other disturbances of extraocular motion were frequent. They usually occurred in association with severe cerebral damage. In one instance, the only evidence of neurologic disturbance was a slight spontaneous lateral nystagmus. This patient had widespread hemorrhage and necrosis of both parietal and occipital lobes. The frequency of nystagmus is in marked contrast to the rarity of cerebellar necroses and hemorrhages. The necroses and hemorrhages responsible for nystagmus in sinus thrombosis seem to be cortical in location, especially in the parietal and occipital lobes rather than in the cerebellum itself. The Babinski sign and its modalities were frequently positive, though many of the patients were too young for this to be of significance. Cranial nerve palsies were very exceptional.

From the foregoing discussion, it may be concluded that no single neurologic sign can be depended upon to establish a diagnosis of sinus thrombosis. However, the development of any neurologic symptoms in an infant with severe hyperthermia who has or is recovering from an acute nutritional disturbance should suggest the possibility of dural sinus thrombosis. The statement has often been made that thrombosis of cerebral veins may be initiated by convulsions due to a variety of causes. If this is true (the evidence is not convincing) there is a possibility that thrombi which have formed in small cerebral veins during convulsive seizures might be propagated eventually into the dural sinuses. At the Infants' and Children's Hospitals there is an opportunity to study the brains of infants and children who have had convulsions from a large number of causes. No evidence has become apparent which would lead us to believe that convulsive seizures initiate thrombi in cerebral veins. So far as the present series is concerned, several patients with thrombosis of cerebral veins and dural sinuses had no convulsions at any time during their illness. In several other patients there was evidence, confirmed by repeated lumbar punctures, that the thrombosis preceded the onset of convulsive seizures by at least one or two days. For these reasons, we feel justified in concluding that, in general, thrombosis of the cerebral veins and dural sinuses may cause convulsions, but that convulsions in themselves cannot be accepted as a cause of sinus thrombosis.

Patients with the clinical syndrome described above have usually died within one to five days after onset of the neurologic disturbances. A few have lived from ten days to one month. Of the two who survived longer, more will be said in a subsequent report in connection with an additional instance of different pathogenesis. The patients living ten days to one month have been critically ill during that time; they have

had high fever, often sustained in the region of 106° F., repeated convulsions, and disturbances of muscle tonus. The following patient is an example of this type.

CASE 2.—J. S., a nineteen-month-old, white, female infant was admitted to the hospital because of fever and diarrhea. The patient developed satisfactorily and appeared well until five days before admission. At that time, she began to vomit 3 or 4 times a day after feedings. There were 4 green, watery stools per day and a fever of 102° F. After three days the vomiting stopped but the diarrhea and fever persisted. On admission, the patient appeared hypertonic and somewhat undernourished. The pupils were normal in shape and reaction. There were no changes in the optic fundi. The heart, lungs, and abdomen presented no abnormalities.

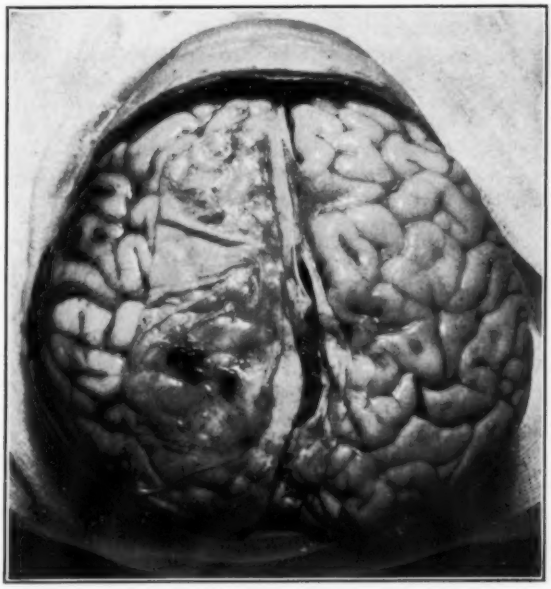

Fig. 3.—Photograph of brain after removal of the calvarium. This shows a thrombus occupying the middle fifth of the superior longitudinal sinus (Case II). There is much evidence to show that this region is the elective site of initial formation for thrombi unassociated with sepsis or surgical procedures. An intradural hemorrhage is also shown.

The anterior fontanel was open. The tendon reflexes of the arms and legs were equal but hyperactive. Chvostek's, Kernig's, and Babinski's signs could not be elicited.

Despite two transfusions, the child became worse for two days. There were 9 watery bowel movements each day. However, on the third day, she began to take fluids eagerly and her general condition improved. A lumbar puncture at this time showed fluid under normal pressure with a slight xanthochromic tinge. The Pandy test was negative; the sugar content normal. The total protein was 30 mg. per cent. The cell count was 2 monocytes per cu. mm. There was no growth on culture. On the morning of the fourth day, the patient had a series of severe generalized convulsions which were terminated after thirty minutes with ether. The optic fundi showed engorgement of veins. The convulsions recurred at intervals of two to three

hours. Between convulsions, the patient was comatose most of the time. By evening of the fourth day there was slight choking of the optic discs. The temperature varied from 102° to 104° F. Lumbar puncture showed grossly bloody spinal fluid with marked xanthochromia after centrifuging. The Pandy test was strongly positive. The sugar content was normal. The total protein was 150 mg. per cent. Microscopic examination showed 32,000 red blood cells and 330 white blood cells. Of the white blood cells, 60 per cent were polymorphonuclear leucocytes; the remainder, large mononuclear cells, at times containing phagocytosed material. Repeated lumbar punctures each showed grossly bloody fluid. The patient continued to have several convulsions each day. Some of these were limited to the right side of the body or of the face. The choking of the discs receded. The clinical course was progressively downhill. Death occurred on the fifteenth hospital day, eleven days after the onset of the convulsions. The involvement of the central nervous system probably antedated their appearance because the spinal fluid on the day before their onset was xanthochromic.

Postmortem examination showed extensive sinus thrombosis. In the superior longitudinal sinus there was an antemortem thrombus 4 cm. in length beginning at the junction of the anterior and middle thirds and extending backward. It was organized partially. The inferior longitudinal sinus, the torcular Herophili, the straight sinus, the left lateral sinus, and the opening of the right lateral sinus were filled with antemortem thrombi. These showed less evidence of organization than those in the superior longitudinal sinus. The great vein of Galen was completely thrombosed. There were no thrombi in the cerebral veins. The blood vessels over the cerebral cortex and in the falx showed very marked congestion. There was an area of subarachnoid hemorrhage (5 by 7 cm.) over the left temporal lobe and the inferior portion of the parietal lobe. The hemorrhage proved to be partially organized when examined microscopically. The surrounding cerebral cortex presented extensive brown discoloration. There was an area of hemorrhage measuring 1 by 1 cm. beneath as well as in the dura overlying the left parietal cortex. It was partially organized. Section of the brain showed an area of cortical hemorrhage and softening beneath the central portion of the area of subarachnoid hemorrhage. This measured 4.6 by 5.1 cm. and involved a large part of the temporal lobe.

SPINAL FLUID FINDINGS

Lumbar puncture furnishes very valuable assistance in the diagnosis of sinus thrombosis. If the spinal fluid is secured very early after formation of the thrombus it may be clear, under slightly increased pressure, and normal in cellular content. Within a few hours, however, blood without evidence of red cell disintegration usually appears in the cerebrospinal fluid obtained by lumbar puncture. Many physicians would be inclined to dismiss these findings as the result of trauma during the procedure of lumbar puncture. In such instances repeated examinations may be necessary before the diagnosis can be established. If the fluid is secured a little later in the disease from a patient with superior longitudinal sinus thrombosis, the picture is much more definite. There is marked elevation in spinal fluid pressure in about half the cases while it is slightly elevated in the remainder. The fluid is xanthochromic when obtained, or grossly bloody at the time and xanthochromic after centrifugalization. The globulin test is strongly positive; the sugar content is normal. Microscopic examination shows 10 to 1,000 red blood cells or more per cubic millimeter with white blood cells in

proportions found in the circulating blood. However, there may be a slight absolute and relative increase in the proportions of polymorphonuclear leucocytes in the absence of any demonstrable infectious agent. This is due to the well-known inflammatory response of the meninges to the presence of extravasated blood.

PATHOLOGIC CONSIDERATIONS

The localization of thrombi in the 31 instances which could not be attributed directly to bacterial infection or surgical procedures was as follows: superior longitudinal sinus 31; superior cerebral veins 15; lateral sinus 17; straight sinus 10; great vein of Galen 7; cavernous sinus 2.

The most striking feature is the involvement of the superior longitudinal sinus in every instance. When the other sinuses were occluded the most extensive thrombosis was always in the superior longitudinal sinus. Histologic examination showed as great or greater degree of organization in the superior longitudinal sinus than elsewhere. Inasmuch as the thrombi were continuous, it seems reasonable to suppose that the other venous channels became occluded by propagation of a thrombus originally formed in the superior longitudinal sinus. Several early thrombi were restricted to the middle one-fifth of the superior longitudinal sinus. Organization, when present, was most pronounced in this region. In two instances, careful study of serial blocks of the sinus containing thrombi showed organization only at this point, though the remainder of the superior longitudinal sinus contained unorganized, though definitely antemortem, thrombi. For these reasons, it seems probable that the middle one-fifth of the superior longitudinal sinus is the elective site of initial formation of the thrombi.

These findings stimulate an inquiry into those local and general factors which might predispose the middle fifth of the superior longitudinal sinus to the formation of thrombi. Inasmuch as veins elsewhere in the body in these patients were not thrombosed, it seems justifiable to assume that local conditions are of great importance. There are certain anatomic arrangements of veins in this locality which tend to interfere with efficient flow of blood. The superior cerebral veins entering the sinus in this region are so directed that blood is emptied into the sinus in a direction more or less opposed to the direction of blood flow within the sinus. The sudden widening of the sinus and the complexity of the lacunar pockets at this point also favor stagnation and eddy formation. Furthermore, the depression of the anterior fontanel resulting from severe dehydration increases the angulation of the superior longitudinal sinus in this region. This assumes particular significance when it is considered that this form of sinus thrombosis has by far its highest incidence in infants with an open anterior fontanel. It was open in all of the patients in this series. Mechanical factors which favor the stasis of blood do not, of themselves, ordinarily bring about thrombosis. In these

patients, a concentration of blood resulting from depletion of body fluids and loss of plasma may play an important rôle. The evidence for and against the occurrence of thrombosis in the absence of endothelial injury has been summarized elsewhere.[1] If chemical alterations in the blood, such as those occurring in association with acute nutritional disturbance, impair the viability of the endothelium, the injury is of such a nature as to avoid detection microscopically either in the sinuses or elsewhere in the body. In view of the well defined elective site of origin and of its occurrence at an age when growth processes in cerebral tissues are ac-

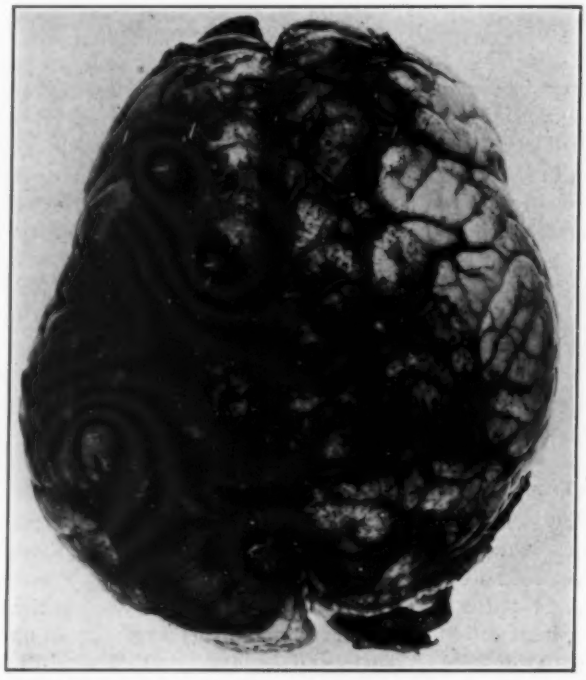

Fig. 4.—Extensive subarachnoid hemorrhage resulting from thrombosis of the superior longitudinal sinus. There are numerous superior cerebral veins distended with thrombi.

tive, one is led to speculate whether or not alterations in the blood during its flow through the brain may be of importance.

The localization and propagation of sinus thrombosis unassociated with sepsis in the ordinary sense or with surgical procedures assume additional importance when the character of injury to the brain is considered. Thrombosis of the lateral sinuses alone, as pointed out previously, did not produce intracerebral hemorrhage or necrosis. Death in these patients resulted from bacteremia, meningitis, or retrograde propagation of the thrombus into the superior longitudinal sinus. In the group under discussion, however, thrombi were found in the superior longi-

tudinal sinus in every instance. Of these, cerebral damage detectable grossly and microscopically was present in 21 instances (67.7 per cent). A summary of the distribution and character of the lesions follows:

Dura and Subdural Space: A small amount of extravasated blood was occasionally found among the dural fibers beyond the wall of the sinus. In two instances a moderate amount of clotted blood was encountered in the subdural space. In one patient, there was a large intradural hemorrhage measuring 3 by 3 cm. in the left parietal region.

Subarachnoid Space: In all 21 instances in which pathologic changes were demonstrated in the brain, there were subarachnoid hemorrhages of variable size and number. These were usually extensive and often bi-

Fig. 5.—Extensive periventricular encephalomalacia (Case I). Intraventricular hemorrhage is often associated with areas of necrosis in this location.

lateral. The blood was found between the arachnoid surface and the fibers of the pia. Very frequently, cerebral necroses with or without hemorrhages were found beneath the areas involved by the subarachnoid hemorrhages, but often there was a narrow rim of intact brain tissue between the two. The veins in the subarachnoid space were strikingly engorged in every case.

Brain Substance: There were areas of necrosis and hemorrhage in the cerebral hemispheres of 19 patients. The parietal lobes were most frequently involved although lesions were found in almost as many instances in the frontal and occipital lobes. The temporal lobe was involved less frequently. The damage was characterized from place to place by softening or hemorrhage or both. The lesions were usually cortical and subcortical, extensive and bilateral. The basal ganglia were

affected in 10 patients. In the numerous small cortical necroses unassociated with hemorrhage, the first and second cortical layers often

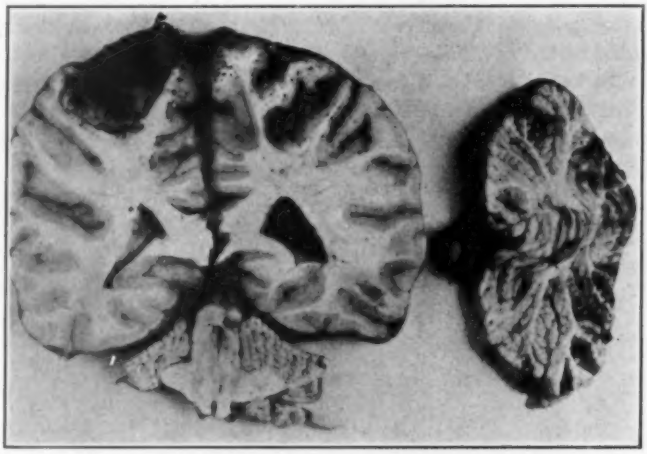

Fig. 6.—The figure shows extensive cerebral damage resulting from thrombosis of the superior longitudinal sinus and its tributary veins. Over the cerebral cortex, there is extensive subarachnoid hemorrhage. Large and small areas of necrosis and hemorrhage are seen through the cortical tissue, mostly in the gray matter. Intraventricular hemorrhage is present. There is some subarachnoid hemorrhage over the cerebellum.

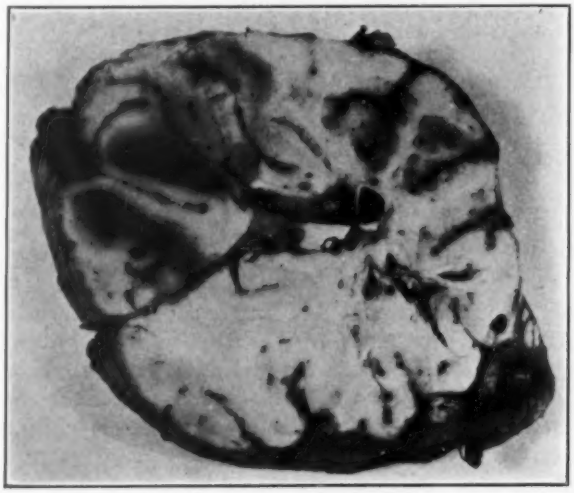

Fig. 7.—Photograph at approximately twice natural size to show the small necrosis so frequently seen when the superior longitudinal sinus is thrombosed. These are found in both gray and white matter. Areas of hemorrhage are seen in the cerebral tissue and subarachnoid space.

escaped involvement. The larger necroses were usually associated with hemorrhage. In the smallest necroses, hemorrhage was rare. The instances in which injury to cerebral tissues was most severe were those

in which the thrombi in the superior longitudinal sinus extended into its tributary cerebral veins. Thrombi in the great vein of Galen and in

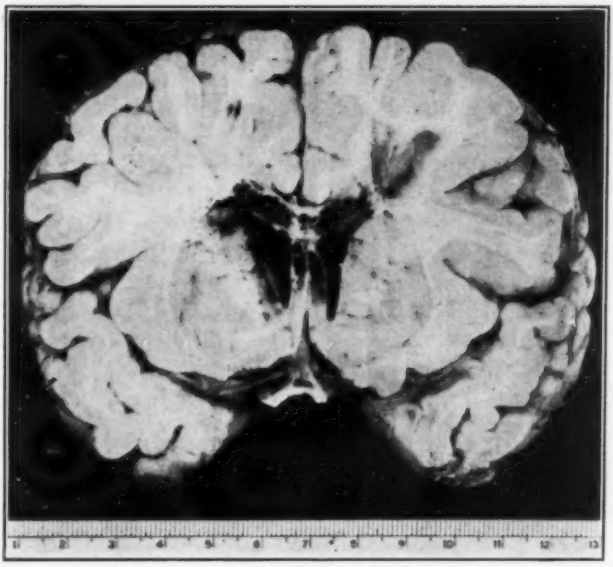

Fig. 8.—Hemorrhages in the corpus callosum and septum pellucidum in a patient with thrombosis of all dural sinuses.

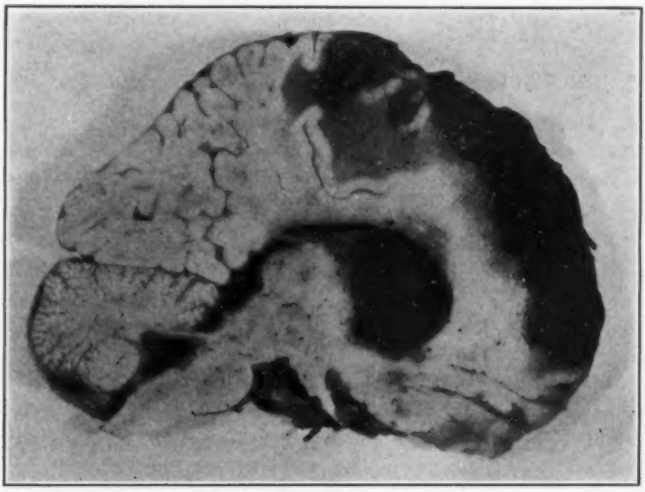

Fig. 9.—Hemorrhage and necrosis of the cerebral cortex resulting from thrombosis of the superior longitudinal sinus and its tributary veins. There is a large amount of blood in the lateral ventricle and also in the fourth ventricle.

most of the dural sinuses were present when areas of hemorrhage and necrosis were found in the choroid plexus and in the preventricular

tissues. There was a small hemorrhage in the cerebellum of one patient. Hemorrhages into the pons and midbrain were rare. There were no intramedullary hemorrhages. Intraventricular hemorrhage was usually found when there were extensive periventricular necroses involving the ventricular walls or when the straight sinus and great vein of Galen were occluded. Intense cerebral edema and a prominent pressure cone were found only when thromboses were extensive and of several days' duration.

Microscopic Findings: The lesions in the most rapidly fatal cases showed complete loss of normal structure of tissues involved. The regions were occupied by necrotic tissue fragments and large masses of red blood cells. Vessels were filled with thrombi. In instances of longer duration, there were evidences of repair. The extravasated red blood cells had partially degenerated. Hemosiderin and lipoid droplets were found in compound granular corpuscles. Proliferation of astrocytes was rather slight and was confined to the margins of the lesions. Thrombi, partially or completely organized, were found in many vessels. Newly formed capillaries were seen in the zones of necrosis in small numbers; these grew in mostly from vessels in the leptomeninges and were accompanied by occasional collagen fibers. Study of the sinuses themselves showed that all the thrombi were antemortem. The sinuses from patients whose clinical course was very brief contained unorganized thrombi. The fibrin was arranged in laminated manner and platelet columns could be identified. In thrombi of longer duration, there was evidence of organization by the ingrowth of fibroblasts. Newly formed capillaries were found in only a few of the thrombi in this group.

SINUS THROMBOSIS IN CHILDHOOD AND IN ADULT LIFE

Sinus thrombosis in infancy is a frequent diagnosis at necropsy while in adults it occurs rarely. In early life the number of instances at the Infants' and the Children's Hospitals varied in the period 1926-1936 from 3.6 to 9.1 per cent of all necropsies in which there was permission to examine the brain. Many of the instances in adults reported from other hospitals have occurred as a complication of sepsis, the thrombi extending by tributary veins to the sinuses from infected foci in the upper lip, nose, or orbit. There were no instances secondary to infectious processes in these regions in the present series. However, cellulitis of the scalp presumably initiated thrombosis in 7 of the patients by much the same process. The latter lesion is comparable especially to a condition of adults which occasionally causes sinus thrombosis. Carbuncles of the neck sometimes extend over the occipital region of the skull and reach the sinus by that route. Thrombosis of the lateral sinuses as a result of otitis media and mastoiditis occurs in adults as well as in children. In infants it is assumed that the infection usually extends directly from the tympanic space to the jugular bulb. This form of sinus thrombosis is far less serious than involvement of the

superior longitudinal sinus insofar as the degree of cerebral injury is concerned. The control of infection is the major problem, which is somewhat simplified by the accessibility of the lateral sinus to surgical approach. Sinus thrombosis occurs in conjunction with bacteremia and meningitis in adults, but less frequently than in young children. Thus sinus thrombosis referable directly to sepsis and perhaps to trauma has many similarities in both age periods. However, the large group of infants in which sinus thrombosis cannot be directly attributed to either of these causes has no parallel in later childhood and adult life. It is to this group that the present study has been largely devoted.

SUMMARY

A study has been presented dealing with 30 instances of thrombosis of the dural sinuses in infancy and childhood. These have been tabulated in connection with 50 instances previously reported[1] forming a total series of 80 cases.

Of these, 42 cases were associated with various forms of sepsis: meningitis, scalp infections, otitis media, mastoiditis, and bacteremias without meningeal localization. Four instances followed surgical procedures.

Thirty-three patients presented no evidence of infection of the central nervous system or blood stream. They were all infants under thirty months of age. The illness began with an acute nutritional disturbance usually followed after a period of days or weeks by evidences of meningeal irritation, marked hyperpyrexia, and convulsions or other abnormal neurologic manifestations. Some infants died without any evidence of neurologic disturbance. In all of these patients, the superior longitudinal sinus was thrombosed in entirety or in part with variable involvement of other sinuses and cerebral veins. Twenty-one of these patients presented hemorrhages into the meninges associated in 19 cases with intracerebral hemorrhage and necrosis. Some of the patients succumbed within a few hours after the onset of the symptoms referable to involvement of the central nervous system. A few lived for ten days to one month. Finally, two patients recovered from their acute attacks and died later with organized and canalized thrombi in their superior longitudinal sinuses. These together with another patient with similar thrombi of different pathogenesis, form the basis of a separate report. This peculiar "nonseptic" type of sinus thrombosis has no counterpart in adult life and largely accounts for the much greater incidence of dural sinus thrombosis in early life than in adult life. The usual severity of the brain injury resulting from occlusion of the superior longitudinal sinus, the protean character of the associated clinical picture and its frequent occurrence make its recognition a matter of importance in neurologic diagnosis in childhood.

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EPIDEMIC DIARRHEA OF THE NEWBORN

II. Control and Prevention of Outbreaks in Hospital Nurseries

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IN COLLABORATION with Rice and Best, we[1] recently summarized our experiences with epidemics of highly fatal diarrhea of unknown etiology affecting newborn babies during their period of customary care in lying-in institutions of New York City. During the period from July, 1934, to December, 1936, inclusive, sixteen outbreaks occurred in the nurseries of eleven hospitals. Among 3,672 liveborn babies, 505 known cases of the disorder developed with a morbidity rate of 14 per cent. Two hundred and thirty-four known deaths resulted, the mortality rate, based on the number of infants exposed, being 6 per cent, and the case fatality rate of those stricken 46 per cent. These rates were exclusive of stillbirths and of the neonatal deaths that are usually identified with maternity services.

Epidemic diarrhea of the newborn is a unique disease entity whose clinical picture is that of a severe intestinal intoxication. It is accompanied by watery yellow stools, abdominal distention, precipitous loss of weight, drowsiness, marked dehydration, toxicity, and shock. Early in the course of the disease there is little or no fever. Vomiting is not a prominent symptom, and blood, mucus, and pus are unusual in the stools. Central nervous system manifestations are rare. Laboratory examination of the blood reveals severe degrees of acidosis and unusually high concentrations of its constituents. The earliest cases develop in but two days after birth, but other babies may become ill as late as the twenty-first to thirtieth day, depending upon the time of exposure. In severe cases death may ensue in twenty-four hours or in five days to one week, terminal complications such as otitis media and pneumonia meanwhile intervening in the latter group. In mild cases recovery takes place in two to three weeks. In general, the prognosis is exceedingly unfavorable.

Epidemiologically, the disorder involves only newborn infants during the first four weeks of life. There are no apparent sex differences in the incidence of the disorder and babies of all races and nationalities are equally susceptible. In addition, no definite seasonal trend in prevalence has been noted. Nor is there any relationship between the incidence of the disorder and the state of nutrition of the infants, or in the type of feeding the infants receive. Autopsy examination characteristically shows a marked disproportion between the overwhelming clinical severity of the disorder and the few pathologic tissue changes. In our experience,

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bacteriologic cultures and virus studies have thus far been uniformly unsuccessful in revealing an etiologic agent.

Since our preliminary report, we have observed further outbreaks in other hospital nurseries, indicating that the disorder is still actively prevalent. We have also received reports of its occurrence in cities other than those mentioned in our first paper. We hope to discuss these additional epidemics in a subsequent comprehensive survey. In the present paper the problem of control and prevention will be considered, not only specifically in connection with this disease but also more broadly with reference to the general lowering of morbidity and mortality in nurseries of lying-in institutions.

In recent years, public health authorities have taken pride in the belief that the incidence of diarrheal disorders among infants and older children has been successfully controlled by present-day methods of preventive medicine. It is true that much has been accomplished in reducing deaths resulting in the past from so-called "summer complaint." Yet, as has been noted by Sauer,[2a] the report of the Health Section of the League of Nations[3] indicates that in all countries diarrheal disorders are still outstanding causes of death among infants and children. This fact is also borne out by the statistical survey by Bolduan and Weiner[4] on infant deaths in New York City for the past one hundred years, and by the records of the New York City Health Department.

A study of Table I on infant statistics of this city shows that during the ten-year period 1926-1936, there has been a steady decline in the total number of births. The stillbirth ratio to 1,000 livebirths has remained essentially constant and is still far too high. Although during the ten years mentioned a marked lowering is shown in the death rate of infants under one year of age, yet practically no downward trend is noted in the mortality rate of infants during the neonatal period, that is, the first month of life. Of importance, too, is the fact that a persistent residue of deaths from diarrheal disorders is still evident in both age groups. In fact, the trend of the death rate from diarrheal disorders among infants under one month of age seems to be rising since 1932.

It should also be remembered that the data in the table are not entirely complete, for at times the diagnosis of enteritis is erroneously stated on death certificates as being the contributory or complicating cause of death rather than the primary cause. Hence, a considerable number of deaths resulting primarily from diarrheal disorders are listed in other categories. The members of the White House Conference on Child Health and Protection give due recognition to this prevalent inaccuracy in diagnosis by calling attention to the meaningless conditions that are often listed as being the cause of death of infants during the newborn period.[5] The need for greater accuracy and precision in diagnosis and more uniformity and completeness of data on birth and death certificates are also stressed by the recent reports of Walker[6] and of Tandy.[7] The

TABLE I

SUMMARY OF COURSE OF INFANT MORTALITY FROM DIARRHEAL DISORDERS IN NEW YORK CITY DURING TEN-YEAR PERIOD FROM 1926 TO 1936

YEAR	TOTAL NUMBER LIVEBIRTHS	TOTAL NUMBER STILLBIRTHS	RATIO TO 1,000 LIVEBIRTHS	NUMBER DEATHS UNDER ONE YEAR	RATE PER 1,000 LIVEBIRTHS	NUMBER DEATHS UNDER ONE MONTH	RATE PER 1,000 LIVEBIRTHS	NUMBER DIARRHEAL DEATHS UNDER ONE YEAR	RATE PER 1,000 LIVEBIRTHS	NUMBER DIARRHEAL DEATHS UNDER ONE MONTH	RATE PER 1,000 LIVEBIRTHS
1926	125,515	6,054	48.2	8,509	67.8	4,058	32.3	846	6.7	92	0.73
1927	128,889	5,895	45.7	7,210	55.9	3,859	29.9	651	5.0	77	0.59
1928	126,332	6,121	48.5	8,280	65.5	4,022	31.8	893	7.0	122	0.97
1929	124,404	5,726	46.0	7,281	58.5	3,770	30.3	751	6.0	115	0.92
1930	122,811	5,700	46.4	7,030	57.2	3,753	30.6	768	6.2	124	1.01
1931	115,621	5,579	48.3	6,472	55.6	3,347	28.9	506	4.3	66	0.57
1932	109,878	5,396	49.1	5,594	50.9	3,228	29.4	418	3.8	80	0.72
1933	103,500	5,347	51.7	5,508	53.2	3,099	29.9	499	4.8	119	1.15
1934	101,239	5,070	50.1	5,287	52.2	3,154	31.2	532	5.2	119	1.17
1935	100,657	4,902	48.7	4,790	47.6	2,934	29.1	487	4.8	155	1.54
1936	98,507	4,994	50.7	4,464	45.3	2,731	27.7	513	5.2	177	1.79

investigations of the New York Academy of Medicine Committee on Public Health Relations in connection with stillbirths,[8] the report of the White House Conference Committee on fetal and newborn morbidity and mortality[9] and the recent article by Rice,[10] attest to the invaluable rôle played by accurate statistical data in campaigns to eradicate avoidable infant deaths.

In our preliminary report, we stressed the difficulties involved in arriving at an etiologic diagnosis bacteriologically and pathologically in the disease which we have designated clinically as "Epidemic Diarrhea of the Newborn." Therefore, until there is a better understanding of this syndrome, as well as of other diarrheal disorders of infancy and childhood, greater reliance must be placed on more adequate means of nursing and medical care in the prevention of morbidity and mortality from this group of diseases. Particularly is this true in view of our present lack of efficient specific sera or vaccines for treatment. Brenneman[11] states: "It is better practice to permit a baby to get well without a diagnosis than to have a meticulous diagnosis confirmed at autopsy." One may perhaps be permitted to add that it is even better practice to make wholehearted attempts to prevent disease in infants than to be forced to study the effects of disease processes in sick and dead babies.

While dealing with the epidemics of diarrhea, the first outstanding impression gained was the lack of definite, well-organized, and coherent plans for the nursing and medical care of the newborn. As has been pointed out by the White House Conference Committee,[5] much is taken

for granted on obstetrical services, the newborn infant being regarded as an unavoidable by-product of delivery demanding attention only if manifest disease develops. The urgent necessity for giving this phase of infancy our earnest attention has been brought out also by the report of American College of Surgeons Conference on Hospital Standardization.[12] This report showed that in 1935, one-third of the babies born in this country were delivered in hospitals. The earlier investigations of the New York Obstetrical Society Committee[13] on maternal care have served to indicate that in lying-in hospitals considerable variations exist in nursing and medical technique, administrative policies, and physical arrangements.

A summary of the various defects observed during our surveys of the obstetrical services need not be detailed here. Reference may be had to the several reports previously mentioned. In brief, these inadequacies relate to the present physical arrangements of maternity and nursery wards and to their mechanical equipment, as well as to the lack of attending personnel. Greater attention is directed to economy of conducting maternity and newborn services than to the question of efficiency and adequacy of service.

CONTROL OF OUTBREAKS

When the early outbreaks of epidemic diarrhea of the newborn occurred in the hospitals of this city, unusually high morbidity and mortality rates were experienced, due to lack of acquaintance with the clinical syndrome and failure of recognition of the primary cases. Maternity services therefore continued in full activity, admitting newborn babies to infected nurseries, thereby increasing the number of possible contacts. In addition, the disorder was not a reportable one, and consequently the outbreaks gained considerable headway before being brought to our attention.

As a preliminary measure in the control of the disease, the Sanitary Code of New York City was therefore amended to include as a reportable condition all cases of "Diarrhea in the Newborn up to three weeks of age occurring in a hospital giving maternity service." The terminology was put broadly to take care of all types of diarrhea, primary or secondary, in order to determine by early investigation the existence of the epidemic form of the disease. In this way, prompt measures are instituted for the control of an outbreak in a nursery. In addition, careful check is made of all death certificates of infants dying under one month of age throughout the city. Each death is traced to the institution of birth regardless of the given cause of death, and the accuracy of the diagnosis ascertained.

We are convinced that in lying-in institutions where early and complete precautions are taken, morbidity and mortality from the disease are lowest. At present, immediate closure of maternity wards and nurs-

eries for the newborn is ordered. Services are suspended until it is certain that no new cases will develop among contacts and until the nurseries and the pediatric wards have been cleared of all sick newborn infants. Provisions are made for the isolation of all primary and secondary cases. All newborn contacts are observed for a minimum period of three weeks before being discharged as normal. Scattering of sick infants is thus avoided and early treatment can be speedily begun in new cases. The adoption of a technique of "aseptic nursing" is insisted on, as well as the complete segregation of the maternity floor from the rest of the hospital with regard to formula rooms, diet kitchens, and laundry and sterilizing facilities.

In addition, the entire physical equipment of the maternity service is routinely inspected for sanitary defects. Cultures are taken from every possible source of contamination and from all materials coming in contact with the baby. Likewise, repeated cultures are made of the nasal and pharyngeal secretions and of the stools of all infants and adults, including mothers, attendants, and other personnel. Carriers of any known infectious organisms are excluded as soon as detected.

SUGGESTED METHODS OF PREVENTION

At the present time there is an evident lack of precautions which if observed would aid not only in the prevention of diarrheal disorders among newborn infants in nurseries, but also of other food-borne and air-borne diseases. We are of the opinion that efficient and workable measures can be taken that would prevent such epidemics. The routine care of communicable diseases in hospitals for contagion and the successful efforts by Sauer[2a, b] to combat the spread of diarrheal disorders and other infections among the infants and children at the Cradle of Evanston, Illinois, are outstanding examples of such precautionary measures. The method of Sauer, as evolved by Dr. Gladys Dick, is based on two essentials, namely, sterility of food, and an individual, aseptic nursery technique which eliminates contamination of anything that enters an infant's mouth or nose. In its details the technique embraces the basic principles of surgical asepsis as applied to the routine care of the infants. All attendants are capped and masked, wear sterile gowns, and are required to scrub and disinfect their hands before handling each baby. Nurses who are assigned to feeding the infants are not permitted to dress or diaper the babies. Each infant is kept in an assigned cubicle and everything within a cubicle is sterile or clean for the occupant. All examining instruments and feeding equipment are rendered surgically sterile for each baby. The same individual technique is applied in all its phases to the diet kitchen routine and to its personnel.

However, in attempting to apply this nursery technique to a service for the newborn, we are faced with a very important difficulty. In institutions such as the Cradle, the resident infant and child population

is in the main a stationary one, each individual remaining in an assigned cubicled crib where it is fed and cared for until discharged. To satisfy this fundamental prerequisite on maternity services is impossible, since the newborn infants must be taken to their mothers for nursing many times a day. Hence, there is a continuous and unavoidable shifting of babies from nursery to ward and back again. *It is of prime importance, therefore, that a technique of aseptic nursing be formulated to include all mothers and maternity ward personnel.* Otherwise, the successful application of precautionary measures is endangered. As a result of our experiences in dealing with the outbreaks of diarrhea, we therefore advance for consideration the following suggestions for the care of newborn infants in nurseries:

The Nursery.—a. Every hospital, institution, home, or place for the delivery care of pregnant women should maintain, in good order, two regularly constituted nurseries, one for normal newborn babies and another for the segregated care of prematurely and immaturely born infants and those congenitally debilitated.

b. Separate facilities should be present at all times for the complete isolation of all infected or ill babies. This nursery should be in a division of the hospital completely away from the main section of the maternity floor.

c. The location of the nursery for well babies should be as near as is possible to the maternity ward in order to obviate carrying the infants long distances through corridors. Proper attention should be given to the factors of light and air, as well as of temperature and humidity control. The latter phase of the subject has been critically analyzed by Yaglou.[14]

d. The spacing around each bassinet should be maintained at a minimal distance of two feet on all sides, the only exception being when high glass partitions are provided between the cribs. The suspension of bassinets on single or double-decked pipe racks or on hooks against walls should be prohibited. Each bassinet should be placed on a small individual table having an adjustable side shelf, to be used for the dressing and diapering of each baby. Wherever possible individual cubicles should be used.

e. The elimination of the use of mattresses in the bassinets is recommended. In their stead, easily sterilized folded blankets should be employed.

f. The use of common dressing or diapering tables should be prohibited. This method of caring for infants has long been known to be a great offender in the inception and perpetuation of infectious diseases among infants.

g. Properly labeled individual equipment, such as thermometers, bathing utensils, and the like, should be provided for each baby and kept at the bedside.

h. The only exception to the method of individual equipment is the weighing scale. Redraping with sterile linen should be required before the weighing of each baby.

i. Common or group carriers for taking newborn babies to their mothers for feeding should be prohibited. The method of individual care should also apply to this phase of daily routine.

j. Adequate facilities should be present in a readily accessible anteroom connected with the nursery, providing for hot and cold water, sterilization of all nursery room equipment, as well as containers for soiled linen and diapers and proper disposal of waste.

k. In order that physicians need not enter the nursery, an additional anteroom having facilities for scrubbing the hands should be present for the examination of babies. All tongue depressors, applicators, ear specula, stethoscopes, and other

examining instruments should be thoroughly sterilized after use for each baby. Fresh sterile linen should be placed on the examining table between each examination of the babies.

l. No dry dusting or sweeping should be permitted in the nurseries. All cleaning should be done while the babies are out during feeding hours.

The Laundry.—All nursery linens, diapers, and articles of infant's clothing should be washed and sterilized separately from the laundry of other divisions of the hospital by a different laundry crew. Sterile paper substitutes should be used wherever feasible. The assorted articles of infant's wear, including diapers, should be put up in individual sterile packages, such as those used in surgical dressings, providing sufficient items for a single change at the bedside.

The Formula Room.—a. The formula room supplying the well and premature babies should be as near as possible to the nurseries. This formula kitchen should be entirely divorced from any diet kitchen supplying the sick infants in the pediatric wards or the sick infants in the isolation nursery.

b. Adequate means of refrigeration for formulas and milk should be supplied, in addition to autoclaves for bottles, nipples, bottle caps, and other formula preparation utensils.

c. Simplicity of formulas should be stressed and their preparation done in as few procedures as is possible. Boiled milk is recommended as an added safeguard.

The Maternity Wards and the Delivery Rooms.—a. Every maternity service should maintain at least two wards, one for "clean" cases and another for the isolation of mothers ill from any cause, or infected with such conditions as syphilis or gonorrhea. The latter ward or isolation rooms should be in a part of the maternity floor well separated from the "clean" ward and should be supervised by a separate nursing personnel.

b. In like manner, separate delivery and labor rooms should be provided for "clean" and for "infected" maternity cases. The latter rooms should be completely separated from the former in all their equipment and nursing personnel.

c. Hospitals caring for private maternity cases should have separate rooms set aside on the maternity floor and not be permitted to care for these mothers near rooms housing private medical or surgical cases.

d. No gynecologic cases or operative procedures should be permitted on the maternity floor service.

Accessory Rooms.—In hospitals where ritual circumcision of infants is frequently done, a separate room should be set aside and divided by a glass partition. One side of the room can be used for guests while the circumcision is in progress on the opposite side. As the infants are usually circumcised at the end of the first week of life or about a day or two before being discharged from the hospital, it is recommended that they not be returned to the main nursery. Facilities can be provided for housing them in an isolation cubicle until the day of discharge.

Sanitary Equipment.—There should be adequate facilities in the nurseries, formula rooms, and examining rooms for the scrubbing and disinfection of hands. In addition, receptacles should be present for the immediate disposal of soiled diapers and linen. The plumbing in all utility rooms and the steam sterilizers should be regularly inspected for defects. The sterilizers should be attached to separate water and drainage lines protected with air-brake devices to avoid backflow or siphonage of contaminated material into their pipes and chambers.

The Nursing Staff.—a. Separate nursing staffs should be maintained for the maternity and the newborn services. The nurses should be thoroughly drilled in the care of the newborn and well trained in the technique of aseptic nursing. The staffs should be constant ones and not ever changing. Each nursery should have its own quota of nurses who are not permitted to do duty on any other branch of the maternity service or in any other ward of the hospital; nor should they be allowed to

pass from one nursery to another. The subordinate nurses should be under the guidance and constant supervision of graduate nurses capable of directing a newborn service and aseptic nursery technique in every one of its details.

b. Effort should be made to approximate as closely as is possible the ratio suggested by Brenneman[11] of one nurse to every two babies in the infant wards, both day and night.

c. Nurses or dietitians who are assigned to the formula room should not be permitted to do any other type of duty during their entire period of service in the diet kitchen.

d. No nurse who dresses, bathes, or diapers the babies should feed any newborn baby. Conversely, no nurse feeding babies should be allowed to care for babies in other respects.

e. Nurses who are assigned to feeding infants should wear sterile rubber gloves for each feeding period. The nurse should immerse her gloved hands in a disinfectant solution as she proceeds from baby to baby while handling the bottles. The work of Sauer[28] has shown that pathogenic organisms from the feces of an infected infant, on the nurse's hands, resist washing alone and contaminate other infants, as well as nipples, food, and feeding equipment. Care should, of course, be taken not to allow the disinfectant solution to come in contact with the rubber nipples while they are being attached with sterile forceps to the bottles.

f. Separate nursing staffs should be maintained for infants in the nursery for premature babies and in the isolation nursery for sick infants.

The Medical Staff.—Closer rapport should be maintained between the obstetric and pediatric attending staffs, the newborn service being in charge of the latter group. At all times a well-trained resident pediatrician should be in attendance. The examination of infants should be speeded up and handling reduced to a minimum.

Maternity and Newborn Service Records.—Complete and detailed records should be kept on the progress of all maternity patients and their babies.

Visitors and Visiting Hours.—Visiting periods should not conflict with nursing hours when the babies are taken to their mothers in the wards. All visitors should be required to wear gown, cap, and mask while visiting the maternity patients. Facilities should be provided for checking hats and coats. At no times should any person other than those attending the babies be allowed in the nursery.

Routine Examination of Personnel.—a. All individuals on duty in the maternity or nursery quarters should be examined daily for any nose or throat condition by a regularly assigned physician, and inquiry made whether there has been any cold, sore throat, running nose, or gastrointestinal condition. Any positive evidence or history, no matter how slight, should constitute sufficient reason for the exclusion of that person from the nursery.

b. All permanent nursery and formula room personnel, as well as maternity ward personnel and attending physicians, should have monthly cultures taken of the nose and throat, as well as of the stools, in order to rule out recognizable carrier states.

c. Any attendant absent from duty for any cause whatsoever should have a fresh culture taken before being allowed to return to service.

The Maternity Patient.—a. The expectant mother should be admitted to an isolation room where complete examination and all preliminary procedures are carried out, to ascertain whether she should be placed in the main maternity ward or in an isolation ward in another part of the hospital as an infected case. If there is a history of nose or throat infection, any gastrointestinal upset, typhoid fever or dysentery, gonorrhea or syphilis, that mother should be considered as an infected case until proved otherwise, so that the baby may be isolated immediately for observation. All mothers should have preliminary nose and throat cultures taken, as

well as stool cultures, as a routine procedure. No mother should be transferred to the main maternity ward until the cultures are proved negative for pathogenic organisms.

b. It must be emphasized again that the newborn population in the nursery is not a stationary one, since the babies are taken out at frequent intervals for nursing. It is at this point that the greatest danger lies in breaking down the barriers erected by aseptic nursing against the spread of infection. Therefore, it is of utmost importance that the mothers at all times be included in the routine technique of aseptic nursing. They also should be capped and masked and their beds draped with sterile sheets before the babies are brought to them. The breasts and nipples should be carefully cleaned. At no time should any baby be brought to a mother who is ill from any cause whatever. When a mother is given out-of-bed privileges, she should feed the infant in a special nursing room adjacent to the nursery rather than having the baby brought to the large open ward. It is of course understood that during feeding hours all nurses and attendants entering the maternity ward be required to wear cap, gown, and mask.

The Newborn Baby.—Immediately upon delivery of the baby it should be taken to an anteroom in the delivery room where the proper temperature may be maintained. In this room the baby should be cared for by a specially appointed nurse and physician whose sole duty should be that of attending to the immediate requirements of the newborn infant. Here the preliminary examination of the baby should be made for any possible defects or infections, so that the infant may be transferred to the proper nursery. Isolation is indicated in the event of immediate or subsequent evidence of infection. Once the baby is delivered and the cord and eyes adequately cared for, the supervision of the newborn baby should pass from the jurisdiction of the obstetrician to that of the pediatrician, who should re-examine the baby and prescribe for its feeding and general care. Should the question arise whether the mother be permitted to nurse the infant, consultation should be arranged between both services.

The Aseptic Nursery Technique.—Given the equipment and organization described above, the next step is the application of the principles of aseptic nursing and medical care of the newborn infants. The technique has been discussed above and need not be repeated here. The regulations should apply with equal stringency to any person doing duty on or entering upon the obstetrical floor, whether doctor, nurse, clerk, maid, or porter. Each person should be supplied with a sterile gown, cap, and mask. Attendants handling babies should scrub their hands before proceeding from one infant to another. As has been pointed out by Spencer[15] and by Abramson and Barenberg,[16] any system of aseptic nursing care can be only as good as the level of efficiency set by its operating personnel. A single careless individual will determine the difference between the success and failure of the technique. It is therefore necessary that all members be thoroughly trained in its application and that greatest attention be paid to the minutae of its details.

SUMMARY

During the past few years outbreaks of highly fatal diarrhea of unknown etiology have been occurring among the newborn babies in hospital nurseries both of New York City and elsewhere. As a result of our experience in this connection, we believe that more effective measures should be instituted in the control and prevention of morbidity and mortality from this and other infectious diseases among newborn infants. A review of the vital statistics on infant mortality shows that although success has attended campaigns to eradicate deaths resulting in the

past from "summer complaint," diarrheal disorders still persist in being an outstanding cause of mortality among infants.

There exists an urgent necessity for reconsidering the entire problem of the care of the newborn baby in hospital nurseries. Efforts should be made to arrive at a more uniform, self-contained, and coherent system of organization for maternity and newborn services. Likewise, concerted attempts should be made to study the newborn period of life with greater interest and attention than has been allotted to it in the past, since our present knowledge of this phase of infancy is today too inadequate to cope with all its problems.

As a means of controlling outbreaks of diarrheal disorders in lying-in institutions, the procedures that have been adopted by us are discussed. In addition, various regulations are suggested for the prevention of such epidemics, as well as other infectious diseases, and are based on the technique of aseptic nursing and medical care, involving essentially the principles of stringent surgical asepsis and stressing individual management. The suggestions that have been advanced are by no means fully perfect, but they deserve unbiased trial. We realize that their successful application implies a complete understanding of their aims and a thorough training in their exacting details.

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THE ANTIRACHITIC VALUE OF IRRADIATED EVAPORATED MILK IN INFANTS

An Out-Patient Study

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IN TWO previous studies with small groups of hospitalized infants[1, 2] it was demonstrated that irradiated evaporated milk was an adequate agent for the prevention of rickets in both white and negro infants. These studies were conducted over a period of four and one-half to five months (December to May), in separate wards and under exactly similar nursing and feeding techniques, which only a hospital regime can provide.

Since the fact was established that irradiated evaporated milk supplied adequate protection against rickets in the full-term baby under controlled conditions, the present study was planned with a view to determine the antirachitic value of the same milk under the ordinary conditions of clinic or home practice.

One hundred and eight infants, who for various reasons were weaned at an early age, were selected for the study.* The sex, color, and age distribution are included in Table I. The majority of infants was under three and one-half months of age at the beginning of the study, and no infant was accepted who was over five months of age. The

Table I

Age, Sex, and Color Distribution of Entire Group of Infants at Beginning of Study

Age Months	White		Negro		Totals
	Male	Female	Male	Female	
0 -1	2	5	1	1	9
1 -1½	1	5	1	8	15
1½-2	2	8	2	3	15
2 -2½	6	3	4	6	19
2½-3	0	4	1	2	7
3 -3½	3	3	3	9	18
3½-4	1	2	2	4	9
4 -4½	1	4	2	5	12
4½-5	0	0	3	1	4
Totals	16	34	19	39	108

From the Children's Hospital of Philadelphia.

*We are indebted to Dr. Harriett Hartley of the Child Hygiene Division of the Department of Health, Philadelphia, for valuable assistance in assembling this group of infants, and to Dr. Howard Childs Carpenter and his staff of the Department for the Prevention of Disease, Children's Hospital, for similar assistance, facilities, and cooperation.

study included the months from December, 1935 to May, 1936, a time comparable to the observation periods of the two previous in-patient studies. Each infant was visited by a trained nurse twice monthly, at which visits the mother was supplied with the necessary amounts of irradiated evaporated milk for her infant, and observations were made concerning proper feeding and environmental conditions. The mother also brought her infant at least once monthly to the hospital clinic. At this time physical examinations, measurements, and roentgenograms (one arm and one leg) were made. Wassermann tests and Mantoux tests were performed only when it was deemed advisable. Records were kept of illnesses, regurgitation, number and character of stools. A uniform feeding schedule was adopted as follows:

Appropriately diluted milk with the addition of 5 per cent corn syrup was fed at a level of 55 calories per pound of expected body weight. The milk was well tolerated by all infants and abnormal regurgitation or frequency of stools did not occur. At the fourth month farina or cream of wheat was added, and at the fifth month sieved vegetables and cooked fruit were added. Egg was excluded, while either orange juice or tomato juice was supplied in adequate amounts.

Random samples of the milk employed were assayed at intervals during the study and were found to contain 125 to 135 U.S.P. units of vitamin D in each 14.5-ounce can. As a result of the first examination of the infants, they were distributed with respect to the presence or absence of rickets as shown in Tables II and III.

The slightly larger proportion of negroes will be noted, since there were 58 negroes and 50 white infants in the entire group. Of the 97 nonrachitic infants, 47 were white and 50 were negroes. Disparity between the clinical and roentgenologic findings was as apparent in this study as in the previous in-patient studies. The roentgenogram was used as a sole criterion for the presence or absence of rickets. Drake, Tisdall, and Brown[3] have also pointed out this lack of agreement.

TABLE II

AGE, SEX, AND COLOR DISTRIBUTION OF INFANTS FREE FROM RICKETS AT BEGINNING OF STUDY

AGE MONTHS	WHITE		NEGRO		TOTALS
	MALE	FEMALE	MALE	FEMALE	
0 -1	2	5	1	1	9
1 -1½	1	5	1	8	15
1½-2	2	7	1	3	13
2 -2½	5	2	3	6	16
2½-3	0	4	1	2	7
3 -3½	3	3	3	7	16
3½-4	1	2	1	4	8
4 -4½	1	4	1	5	11
4½-5	0	0	2	0	2
Totals	15	32	14	36	97

TABLE III

GROUP OF INFANTS SHOWING RICKETS AT BEGINNING OF STUDY

AGE		SEX	COLOR	RICKETS AT START	HEALING FIRST NOTED	HEALING COMPLETE
MO.	DAYS					
1	28	M	B	+	?	9 wk.
1	29	F	W	+	8 wk.	15 wk.
2	0	M	W	±+	8 wk.	12 wk.
2	3	F	W	±	7 wk.	12 wk.
2	11	M	B	±	6½ wk.	10½ wk.
3	3	F	B	±	?	15 wk.
3	15	F	B	+	4 wk.	10 wk.
3	21	M	B	+	4½ wk.	6 wk.
4	8	M	B	Healed		15 wk. no signs left
5	0	F	B	+	6 wk.	12 wk.
5	0	M	B	+	?	3½ wk.

RESULTS

Table III summarizes the group of 11 infants who were suffering from rickets at the beginning of the study. It will be noted that none of them showed any marked degree of rickets and that healing occurred in all of them during the course of the study. The average time for complete healing in the entire group was eleven weeks, the shortest time being three and one-half weeks, and the longest time fifteen weeks. As far as could be determined in the course of routine examination, healing began on an average at six weeks.

As has been pointed out in the previous studies and in the reports of others,[4] rickets will heal slowly with irradiated evaporated milk. However, the length of time here noted is evidence of its inefficiency as a healing agent.

Table IV summarizes the group of 15 infants who developed rickets during the course of the study. In eight instances the rickets were considered as barely detectable or doubtful, or plus-minus, and in the other seven instances never progressed beyond a very mild rickets, or plus. Rickets appeared from five to fourteen weeks after the irradiated milk was started. Complete healing was noted in 12 of these infants at the end of the study, while two infants were in the process of healing, and one infant who had barely detectable rickets showed no change. It is of particular interest that only 3 of the 15 infants who developed rickets during the course of the study were negroes, whereas of the 97 infants free from rickets when first observed, 50 were negroes. This difference between the two races in the development of rickets is statistically significant. While this is contrary to the generally accepted opinion as to the greater susceptibility of negro infants, it is in agreement with the findings of Eliot et al.[5] The three negro infants who developed rickets were females. No significant difference in rate of growth, in length, or weight between the 15 infants who developed rickets and the 84 infants who remained free from rickets was appar-

TABLE IV

GROUP OF INFANTS WHO DEVELOPED RICKETS DURING THE STUDY

AGE		SEX	COLOR	TIME AT WHICH RICKETS WAS FIRST NOTED	TIME AT WHICH EVIDENCES OF HEALING WERE NOTED
MO.	DAYS				
0	21	F	W	10 wk. +	14 wk. + healed 18 wk. 0
0	22	F	W	7 wk. ± healed	11 wk. ± healed 14 wk. 0
0	25	F	W	11 wk. +	19 wk. + (healing)
1	13	F	B	14 wk. ± 18 wk. +	21 wk. + healed
1	15	M	W	6 wk. +	9 wk. + healed
1	15	F	W	10 wk. +	14 wk. + healed
1	11	F	B	4 wk. +	7 wk. + healed
2	6	M	W	6 wk. ±	10 wk. + healed
2	6	M	W	6 wk. +	10 wk. + healed
3	15	M	W	5 wk. ±	16 wk. + healing 20 wk. + healing
3	15	M	W	6 wk. +	10 wk. + healed
3	15	M	W	10 wk. +	13 wk. + healed
4	2	M	W	15 wk. ±	20 wk. ± healed
4	11	F	B	6 wk. ± healing	10 wk. ± healed
4	11	F	W	14 wk. ±	19 wk. ± (no healing)

ent. The increases in weights and heights of the entire group of infants were within or exceeded the normal limits as established by Kornfeld.[6]

SUMMARY AND CONCLUSIONS

Of 97 nonrachitic infants fed irradiated evaporated milk, 82, or 84.5 per cent, were completely free from rickets, 14 developed but very mild rickets which disappeared during a five-month period of observation, and one developed very mild rickets which did not disappear. Of the 97 nonrachitic infants, 50 were negroes and 47 were white. It is interesting that of the 15 infants in this group who developed rickets, only 3 were negroes.

Considering these facts, we would, therefore, conclude that this milk is an effective prophylactic antirachitic agent under the ordinary conditions of out-patient practice. This conclusion is in agreement with our previous findings on in-patients fed the same type of milk.

Also in agreement with our previous findings on in-patients is the fact that this milk proved to be an inefficient healing agent, because of the long period of time required for complete healing.

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CRETINOID EPIPHYSEAL DYSGENESIS

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THIS title refers to the formation of epiphyses from multiple loci of ossification. These develop progressively, are probably not normal in composition, and may never become uniform epiphyses if untreated, but will improve with adequate therapy. Dysgenesis is common in the capital epiphyses, is usually bilateral, occurs in other locations, and is confused with the chondrodystrophies described by Legg, Perthes, and others. Not all patients with hypothyroidism develop this type of epiphysis. It is more characteristic of true endemic cretins who are seen infrequently in the United States. The term cretinoid is applied to the thyroid disturbances we encountered.

Langhans, 1897, first described the changes in the peculiar stippling of the epiphyses in true cretins. His work was done on cadavers. Fairbank, in 1927, reported instances of "dwarfism with stippled epiphyses" but failed to recognize the thyroid disturbance. Independently, Seeman and Looser in 1928, published extensive descriptions of the clinical,

TABLE I

CASE 1. A. D.

Age	12 yr. 2 mo.	13 yr. 7 mo.	14 yr. 8 mo.
Height—inches	43	47.7	52.6
Bone age—years	5	6. Less stippling	7. Less stippling
Basal metabolic rate	Uncooperative	23 per cent minus without therapy	27 per cent minus without therapy
Intelligence quotient	50 per cent		46 per cent
Blood—mg. per cent			
Cholesterol	Normal		324 mg. per cent; normal fat fraction
Calcium	Normal		Normal
Phosphorus	Normal		
Phosphatase (Kay units)	14.4	7.1 to 7.8	6.8 to 7.5
Protein		5.74 to 6.09	
Anemia	65 per cent hgb.; quick recovery	None	None
Wassermann	Negative		
Aub study—daily balance			
Calcium	258 mg. loss	340 mg. loss	53 mg. retained
Phosphorus	346 mg. retained	117 mg. retained	156 mg. retained
Excretory channels	Normal	Normal	Normal
Therapy	Thyroid extract gr. ¾ Dicalcium phosphate Viosterol	Somewhat irregular	Continuous

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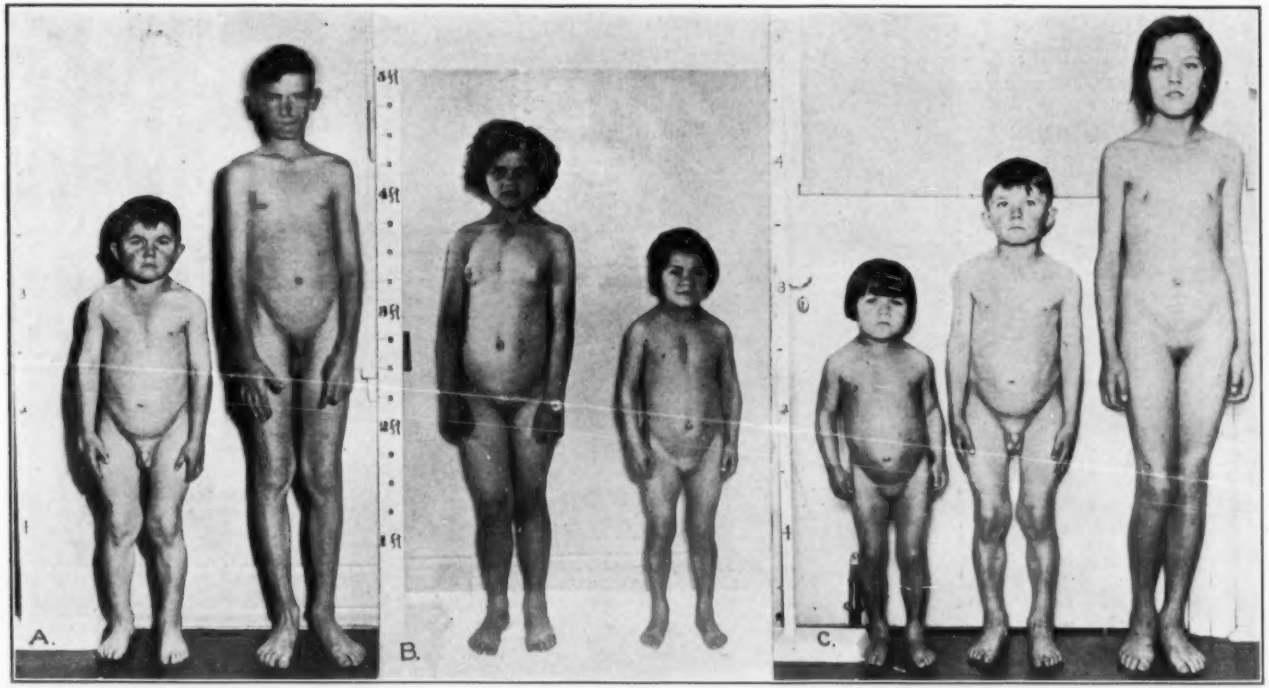

Fig. 1.—*A:* A. D., aged twelve years, before treatment, shown with a normal boy of the same age.
C: E. P., aged eleven and one-half years, before treatment, shown with A. D. and a normal girl of the same age to the right. *B:* E. P., after nine months of thyroid therapy, pictured with a girl of the same age to the left.

pathologic, and roentgenographic phases of the condition. There are no known descriptions or references to the condition in American literature.

REPORT OF CASES

CASE 1.—A. D., a boy, aged twelve years and two months, had marked hyperthyroidism which had not been treated since early infancy (Fig. 1). For several months he had had a waddling gait after several hours of walking. His height was average for six years (45 inches) and his bone age averaged five years. The epiphyses, particularly of the heads of the femurs and humeri, and less notably of the lower ends of these bones, were granular in appearance, and had multiple ossification centers. The other epiphyses were fragmentary (Fig. 2). There was flaring

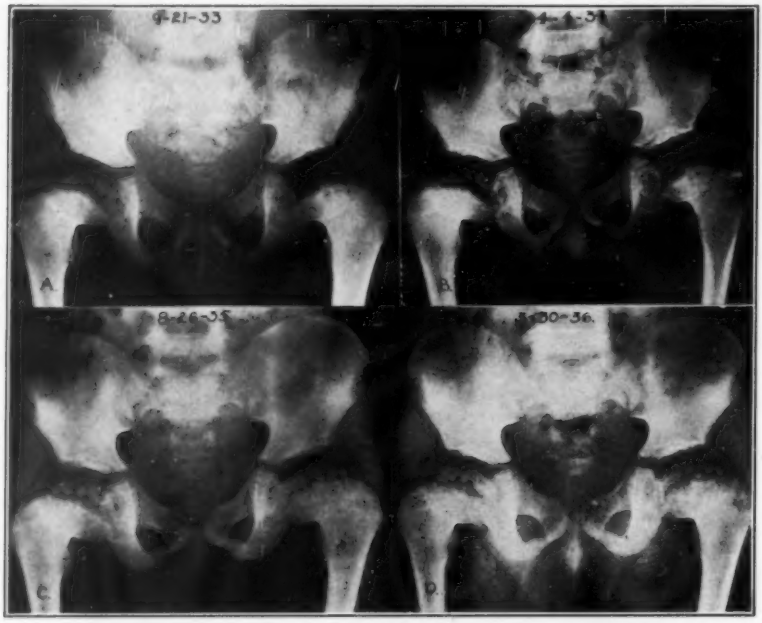

Fig. 2.—A. D. Gradual lessening of stippling occurred progressively. The epiphyses would have formed more normally if the patient had been more faithful to thyroid therapy.

of the costal margins and long bone diaphyseal ends, marked coxa vara, genu varum, maldevelopment of the vertebral bodies, and marked squaring of the skull which suggested old rachitic deformity. The glucose tolerance was normal. The basal metabolic rate could not be obtained because of his lack of cooperation (intelligence quotient 50 to 52). Blood cholesterol, calcium, phosphorus, and Wassermann reaction were all normal; however, the phosphatase was 14.4 Kay units. The calcium phosphorus metabolism test showed a daily loss of 258 mg. of calcium and a retention of 346 mg. of phosphorus; the partition by the excretory channels was normal. The red blood cell count was 3,200,000 and the hemoglobin 62 per cent.

Thyroid substance, ¾ grain daily, was started. He was also given a high calcium, low phosphorus diet. After taking thyroid substance irregularly for one month he complained of great weakness in his hips after playing and had to be carried. For

several days he had crops of purpura on the thighs. The bleeding and clotting time, and platelet and tourniquet tests were normal. The purpura reappeared after resuming the thyroid substance but disappeared with discontinuance of the therapy for several weeks. It has not reappeared with subsequent administration of the same dose. Dicalcium phosphate was added to the diet.

Six months later, at twelve years and eight months of age, he had grown three and three-quarters inches and felt quite well. The basal metabolic rate was 9.7 per cent minus; blood cholesterol was 222 to 353 mg. per cent; a previous anemia was improved; his intelligence quotient was unchanged. There was less tendency to stippling in the formation of his epiphyses and the bone age average was six years.

Fig. 3.—E. P. Compare *A* and *B* noting the improvement of epiphyseal formation within six months. *C* and *D* are further stages of improvement and *D*, particularly, the normally formed capital epiphysis.

A year and one-half after instituting therapy, which he had followed irregularly (only 80 grains of thyroid ingested in four months), he had grown 4.7 inches and he looked a little less cretinoid. His basal metabolic rate after two weeks without thyroid was 23 per cent minus (Reed formula). The bone age was six years and the epiphyseal stippling was less marked than originally. The blood calcium and phosphorus were normal, phosphatase 7.15 to 7.84 units (Kay). The calcium phosphorus metabolism showed a daily loss of 340 mg. of calcium and a retention of 117 mg. of phosphorus. The blood proteins were 5.74 to 6.09 mg. per cent.

At fourteen years and eight months, after two and one-half years of thyroid therapy, only the last year of which he had taken it regularly, he had grown 7.6 inches (height 52.6 inches), his intelligence quotient was 46 and his appearance was not much improved. The basal metabolic rate was 27.3 per cent minus, one week

after stopping therapy. The bone age averaged seven years but the epiphyseal stippling was less. All of the epiphyses were enlarging; the blood cholesterol was 324.6 mg. with normal fat partition, phosphatase 5.8 to 7.5 mg. per cent; blood calcium and phosphorus were normal. He had at this time a daily retention of 53 mg. of calcium and 156 mg. of phosphorus and normal excretory channels (Table I).

CASE 2.—E. P., a girl, eleven and one-half years of age, probably had first developed marked hypothyroidism during infancy (Fig. 1). She had not grown for two and one-third years and her height was average for a four-year-old girl (39 inches). Her bone age was three to six years. The epiphyses for the heads of the femurs were very granular, the appearance being the same as for Case 1. There was a peculiar development of the epiphyses for the metacarpals, and the bone structure of the fifth metacarpal was somewhat unusual, being trabeculated and having a wide shaft (Fig. 3). She had a cretinoid appearance, and had had no thyroid treatment.

Demineralization was progressive in this girl's skeleton before therapy was started, as was demonstrated by the daily loss of 157 mg. of calcium. This loss became greater after the first month of thyroid, dicalcium phosphate, and viosterol medication. The phosphatase was slightly elevated, 9.04 to 9.12 (Kay units).

During the first six months of medication the patient had grown two and one-half inches, more calcium was being deposited in her bones, and epiphyseal lines were more narrow. Epiphyseal stippling, although less, was still present. Nine months after instituting therapy the patient had an attack of pyuria which was found to be a complication of a congenital bilateral hydroureter with hydronephrosis. She had grown five inches (height 44 inches) and her bone age had increased to nine years so that no renal osteodystrophy was likely. Despite continuous therapy of a maximum tolerated dose of thyroid, gr. ¾ daily, the patient at this time had a

TABLE II

CASE 2. E. P.

Age	11 yr. 6 mo.	12 yr. 3 mo.	13 yr. 6 mo.
Height—inches	39	44	44
Bone age—years	3 to 6; stippling; demineralization	9	10. Less stippling
Basal metabolic rate	14 to 40 per cent minus	3.5 per cent minus; no therapy for 2 wk.	30.8 per cent minus
Intelligence quotient	62 per cent		58 per cent
Blood—mg. per cent			
Cholesterol	375	218	196.8; normal fat partition
Calcium	9.9		9.8
Phosphorus	4.3		3.74
Phosphatase (Kay units)	9.04 to 9.12		4.9 to 7.06
Wassermann	Negative		
Glucose tolerance	Very good	Normal	
Anemia	58 per cent hgb. rose to 82 per cent in 1½ mo.		84 per cent hgb.
Aub study—daily balance			
Calcium	157 mg. loss		Normal
Phosphorus	71 mg. retained		Normal
Excretory channels	Normal		
Therapy	Thyroid substance—gr. ¾ Dicalcium phosphate Viosterol Copper and iron started at 11 yr. 10 mo.		No therapy for 3 mo.

myxedematous appearance of the optic nerves and retina which subsequently disappeared. Examination showed a three-year delay in eruption of the permanent teeth, which in addition were erupting in irregular order. There were five retained deciduous teeth. The permanent tooth buds were present. All the teeth seemed to be free from caries.

This patient was faithful to therapy for twenty-one months. She then discontinued it for three months. Two years after our first observations her height remained at 44 inches; the basal metabolic rate was down to 30.8 per cent minus but the bone age had increased to almost ten years. The epiphyses of the femurs were forming normally and only a faint suggestion of stippling was evident. The calcium phosphorus balance was about normal (Table II).

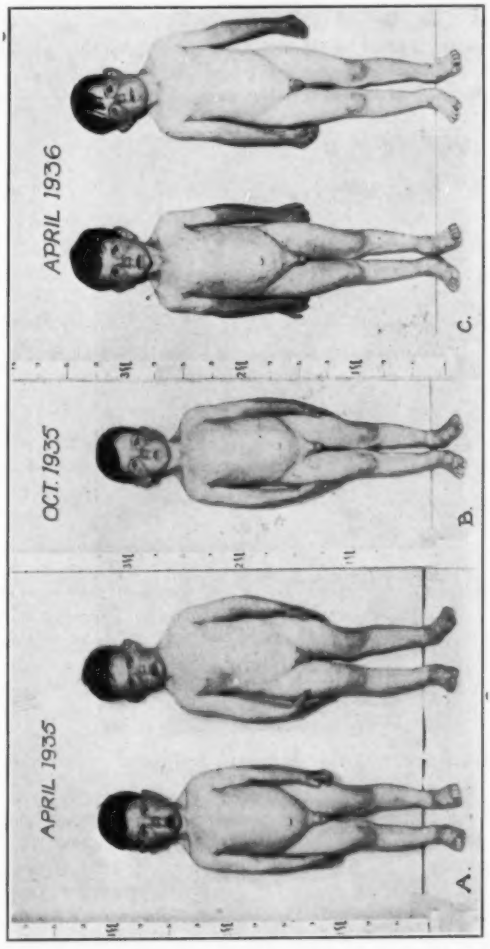

Fig. 4.—*A*: D. R., aged five years, just before thyroid was started, shown with his taller three-year-old brother. *B*: D. R., six months later. *C*: D. R. and his brother one year later. Note the marked physical and mental improvement.

Case 3.—D. R., a five-year-old boy, probably first manifested hypothyroidism at about two years of age (Fig. 4). He had not been growing well for two years and walked with a slight waddle. His height, 37 inches, was average for a three-year-

old. His bone age was about two years. In the ossified epiphyses of the upper extremity, there was an unusual and partially fragmented appearance as though the laying down of new bone had been rather irregular. The heads of both femurs were distinctly abnormal. The calcium was laid down as small, fragmented nuclei of bone over an area less than one cm. in diameter. The roof of the acetabulum appeared distinctly abnormal in that it was shallow with an unusually wide zone of cartilage which had not calcified. The necks of both femurs were distinctly broadened and thickened, having the appearance of coxa vara (Fig. 5).

His physical appearance changed to nearly normal after two months of constant therapy (one-half grain thyroid substance daily and dicalcium phosphate). In six months he grew one and three-quarters inches and the epiphyses aged to four years. The small fragmented nuclei forming the epiphyseal heads of both femurs

Fig. 5.—Definite improvement with thyroid therapy can occur in as short a time as six months. This happened in D. R.

had doubled their former size. Likewise, considerable amounts of bone had been laid down in the roof of the acetabula and over the crests of the ilia. There was likewise a marked increase in the size of the humeral epiphysis of the right shoulder, and there appeared an ossification center for the wrist, metacarpal, and phalangeal bones.

At the end of one year of therapy he had grown 3½ inches and his bone age was between four and five years. Calcium was being laid down in the epiphyses of the femurs in a more orderly manner and from roentgenograms appeared to have increased about 50 per cent over that on entry.

This patient was very faithful to therapy and it was purposely kept at one-half grain daily so that growth would not be too rapid and possibly leave him dwarfed at maturity. His intelligence quotient had increased from 73 to 85, an unusual occurrence in true severe hypothyroidism (Table III).

TABLE III

CASE 3. D. R.

Age	5 yr.	5 yr. 6 mo.	6 yr.
Height—inches	37	38.75	40.5
Bone age—years	2. Stippled	4. Less stippling	4½ to 5. 50 per cent more calcium present
Basal metabolism	Uncooperative		Uncooperative
Intelligence quotient	73 per cent		85 per cent
Blood—mg. per cent			
Cholesterol	Normal		10.5
Calcium	Normal		4
Phosphorus	Normal		
Wassermann	Negative		
Anemia	Hgb. 60 per cent; rapid recovery	None	None
Therapy	Thyroid extract gr. ½ Dicalcium phosphorus Viosterol	Continuous	Continuous

The two following case reports cover longer periods of observation and also show the development of the epiphyses during therapy and the ultimate favorable outcome.

CASE 4.—A. G. (Courtesy of Dr. William Palmer Lucas): This boy had had severe mental and physical hypothyroid stigmata all of his fourteen years. He was only 42 inches tall. The one physical evidence of abnormally stippled capital epiphyses was marked pronation of the feet. The bone age was between four and five years; the basal metabolic rate was 8 per cent minus, intelligence quotient was 18 to 25; blood cholesterol was 388 mg. per cent.

A roentgenogram, March, 1927, showed that the epiphyses of the upper and lower extremities were poorly formed and had an unusually porous appearance; the heads of the femurs were represented by small irregular calcifications.

The usual rapid improvement in skeletal growth during therapy with thyroid extract (grains 3 daily) ensued; he grew 3 inches in the first four months. The examination of the capital epiphyses was done three and one-half years after starting therapy and showed perfectly formed epiphyses but there was a deformity in the shape and angulation of the neck. When last seen in 1932 other developing epiphyses had formed normally.

CASE 5.—(Courtesy of Dr. Hans Lisser). The following cursory data are presented on a patient suffering from cretinoid epiphyseal dysgenesis, who was observed over a period of fifteen years.

H. P., a fifteen-year-old boy, was only 41½ inches tall and had a hypothyroid facies and build. His skull was dolichocephalic. The characteristics of the body and trunk together with marked external and internal genital infantilism and skeletal dwarfism indicated some hypopituitarism. He had the mentality of a seven and one-half-year-old child. His bone age was six years. Only the epiphyses of the heads of the femurs had the irregular fragmented appearance; the flatness of the epiphyses and angulation of the neck at that time (1921) were suggestive of Calve-Legg-Perthes disease. There were no abnormal local physical signs. The condition was first noticed when he was about two years of age.

During the first year of thyroid and anterior pituitary therapy he grew 3½ inches, and his bone age reached ten years. No stippling was detected in the

epiphyses of the wrist, the only area examined. At the age of seventeen and one-half years the os calcis was first examined; it was stippled. It was examined again at twenty years of age and found to have formed homogenously.

After three and one-half years of therapy with thyroid, pituitary, and Didymin (Armour), he had grown 10¼ inches and the bone age was approximately fourteen years. He was then eighteen years of age. This was the first time that the capital epiphyses were found to be homogenous. No epiphyses, subsequently formed, showed stippling. Treatment for four and one-half years resulted in a growth of 14⅝ inches, as compared with a growth of 5½ inches between the ages of ten and fifteen years before treatment was started. When last seen in 1936, fifteen years after the institution of therapy, there was no physical evidence of abnormally formed epiphyses. This is the longest period of observation available for this condition.

DIFFERENTIAL DIAGNOSIS

For many reasons tuberculosis can be excluded. There is no severe pain, fever, leucocytosis, local swelling, heat, or abscess formation. The roentgenograms showed no destructive process. There is progressive new bone formation without sclerosis. Tissue sections are entirely devoid of tubercle or tubercle bacilli.

The condition in the femoral head is nearly always confounded with the epiphysitis of the capital epiphysis described by Calve, Legg, and Perthes. It is true that the roentgenographic picture in both conditions may be nearly identical. However, certain details are different, namely:

	Calve-Legg-Perthes Disease	Cretinoid Epiphyses
Loci of calcification	Not often	Always
Distribution	Usually unilateral	Most frequently bilateral
Course	A destructive process of formerly uniform epiphyses	Not destructive—the epiphysis forms from loci
Pathologic changes	A destructive, aseptic necrosis	Very little if any necrotic change
Response to thyroid substance	None—continues to destroy progressively. Immobilization by cast, rest, or surgery is usually necessary	Healing or cure possible within six months, usually does not require immobilization

Dysgenesis occurs in other epiphyses of the skeleton (Fig. 6). It is often bilateral. Thus we have seen it in both ends of the humeri, ulna, radii, tibia, fibula, and vertebral column. Such a dissemination does not characterize Calve-Legg-Perthes disease. We do not believe that dysgenesis is the concomitant occurrence of the various types of "aseptic necrotic" osteochondritis in the same patient. Furthermore, such osteochondritis does not show any appreciable response to thyroid therapy. The differential points for the capital epiphyses hold for other epiphyses.

THE CLINICAL COURSE

On first discovering these epiphyseal formations one is inclined to expect further changes and even destruction. The persistence of unused cartilaginous masses on the surface of the epiphyses and spongeous bones,

especially on the joint surfaces of the femoral heads, doubtless is the cause of the frequent occurrence of severe forms of deforming arthritis of the joints, with severe destruction of the head of the femur, in adult cretinism. The unossified cartilaginous masses on the surface of the femur cannot bear much weight and this leads to wearing "thread-bare" the surface of the epiphysis. Three of our five cases showed a deformity in the shape and angulation of the neck.

Great improvement follows small doses of thyroid substance even within six months and clinical cure can sometimes be effected in one year. Under therapy a new epiphysis can develop normally without stippling. Thus Case 3, weight 40 pounds, after six months' ingestion of ½ grain of thyroid substance daily, showed great improvement and

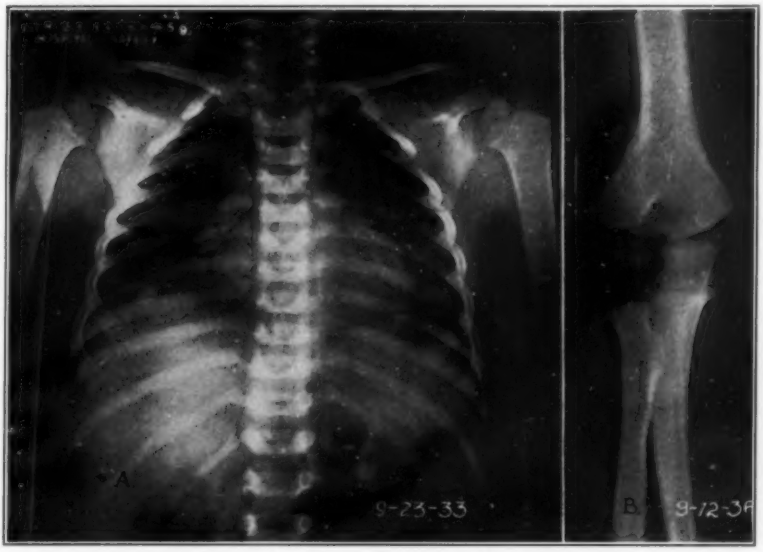

Fig. 6.—Stippled epiphyses are often bilateral and can occur at several sites. Besides the hip, A. D. had these changes in the elbows and the shoulders.

at the end of the year it was estimated that about 50 per cent more calcium was being deposited than before treatment. Purposely the dosage was kept a good deal below the greatest tolerance so that his epiphyses would not age too quickly. Should rapid formation of epiphyses persist for many years the epiphyses might close before the eighteenth year, leaving him more dwarfed than he was destined to be.

Coincidentally, the patients received viosterol, 10 to 20 drops daily, and one drachm three times daily of the following:

Dicalcium phosphate	30/
Lactose	30/
Lemon juice	30/
Water to	**160/**

This supplied 60 grains of dicalcium phosphate daily, probably a normal intake, replacing calcium lost by the action of thyroid substance. Viosterol was used to help in the utilization of the salt. This mixture of dicalcium phosphate has a balanced amount of calcium and phosphorus, is readily absorbed in an acid medium and lactose is added for palatability.

Patients frequently omitted the viosterol and salt mixture and used only the thyroid substance. We feel that the improved formation of the epiphyses was attributable to the thyroid substance.

SUMMARY

In some children having severe hypothyroidism resembling that of the true cretins, many of the epiphyses develop abnormally and have the following characteristics: There are multiple loci of calcification; the calcification is slow; abnormal epiphyses occur in many parts of the skeleton; the distribution usually is bilateral; the process occurs generally in the capital epiphyses; and there may never be normal structure without treatment. When thyroid extract is used normal epiphyses develop in as short a time as six to twelve months. Dysgenesis is frequently mistaken for the chondrodystrophy of Calve-Legg-Perthes disease.

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INTRACRANIAL HEMANGIOMA ASSOCIATED WITH FACIAL NEVUS

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IN RECENT years increasing attention has been given to the study of a well-defined clinical entity, the outstanding manifestations of which are the presence of a port-wine nevus of the face associated with a homolateral intracranial hemangioma, epilepsy, paralysis, and mental retardation. Tredgold[1] applied the term "naevoid amentia" to the syndrome. Yakovlev and Guthrie[2] refer to it as "encephalotrigeminal angiomatosis." Greenwald and Koota[3] were able to collect eighty-two cases from the literature. Since their publication at least two more cases have been reported.[4]

Thus, the condition is not a common one. The following cases are reported primarily for their study value and secondarily in an attempt to draw some tentative conclusions concerning the relationship of the mental retardation and mental phenomena observed to the intracranial vascular anomaly.

REPORT OF CASES

Case 1.—E. W., a white male, aged twenty-one years, was admitted to the Polk State School for Mental Defectives Oct. 4, 1925, because of obvious mental defect. Our records, though not complete at the time of admission, show that at that time he was obese, of a restless and erratic disposition, exhibited a port-wine nevus over the right side of the face, had a left spastic hemiplegia, walked with a hemiplegic gait but was capable of fair locomotion, and was subject to frequent grand mal attacks. His mental reactions were those of a midgroup imbecile (intelligence quotient 30 to 40).

Running notes on his record show a gradual mental and physical deterioration with increased frequency and severity of the grand mal convulsive seizures. He had, within the last three years, many episodes of status epilepticus.

At the present time the patient is a low-grade idiot with an I.Q. below 20. He is untidy and requires constant custodial care. He is subject to almost daily grand mal attacks and periods of status epilepticus occur about once a month.

Physical examination reveals a much emaciated white male with a marked left hemiplegia and left-sided contracture deformities of the arm and leg. Atrophy of the left side of the body is prominent. The patient is incapable of locomotion. He sits with his right hand in his mouth and slobbers constantly. The skin of the right hand is macerated from the constant bathing in saliva. He reacts to all verbal stimuli with an explosive "yes." Otherwise his mental reactions are about nil. A large port-wine nevus is present on the right side of the face. It follows, in general, the distribution of the trigeminal nerve, extends into the oral cavity on the right and involves the gums, cheek, and hard and soft palates. Nasal examination was not made but the patient is subject to frequent attacks of epistaxis from the right nostril. Pupils are equal and equally reactive to light. Eyeground examination was

not attempted. The heart sounds are somewhat distant. No murmurs or arrhythmias noted. Lung fields are clear. Abdominal examination is negative for pathology. Genitals are of normal development. The reflexes on the left side are hyperactive. Left ankle clonus is present.

Laboratory examination reveals no abnormality of the blood picture or the urine. No spinal puncture for diagnostic purposes was deemed advisable. Roentgenograms taken under deep barbiturate narcosis reveal typical roentgenographic shadows suggestive of a calcified intracranial hemangioma on the right side (Figs. 1 and 2). The double contour lines frequently reported are outstanding in this case. There is also to be noted the very large right frontal sinus and antrum.

The past medical history, rechecked by personal conversation with the parents, reveals that the child was born at full period and weighed twelve pounds at birth. The birth was not difficult. The mother states that she had a severe mental shock at three months' gestation due to her presence at a large fire in her neighborhood.

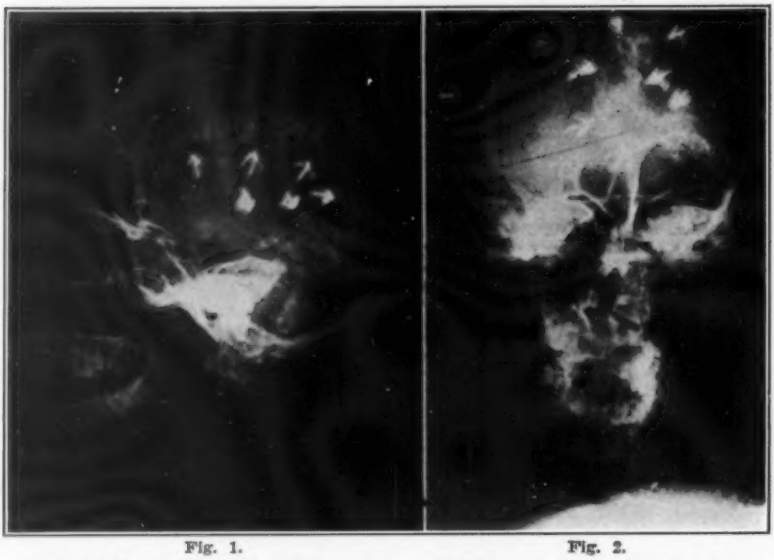

Fig. 1. Fig. 2.

Fig. 1.—Case 1. Lateral roentgenogram. Hemangioma in the right side of the brain.

Fig. 2.—Case 1. Anteroposterior view, note large frontal sinus.

The nevus was present at birth and fitted in general configuration the outline of a hand. At three or four months the patient began having Jacksonian convulsive attacks involving the left side of the body. At six months the child had a period of narcolepsy (?) associated with generalized severe convulsions and anuria. Since that time the convulsive attacks have always been generalized and severe. Until the age of three or four months, when the first convulsive seizure was noted, the child seemed normal in its reactions, though this history is somewhat vague. He began to walk at seven years, with a hemiplegic gait. He said a few words at four years.

The family history reveals a rather poor stock. A second cousin of this patient on the paternal side is a patient in a mental hospital. The paternal grandfather and paternal grandmother were alcoholics. Another cousin on the paternal side is an epileptic. The father and mother are apparently well mentally but not particularly intelligent. A sister of the patient, age twenty-five years, is a cretin. Another sister

is apparenty normal mentally but there is a question of sexual delinquency. A brother, aged twenty-two years, is an epileptic and was examined at our outpatient clinic at our request. His case report in brief is as follows:

A white male, aged twenty-two years, complaining of convulsive attacks occurring about once a month. The attacks always occur at night and are followed by a period of lethargy lasting from twenty-four to thirty-six hours and accompanied by feelings of a religious nature. The convulsions began at the age of seven years during an illness diagnosed as pneumonia. At that time and following the pneumonia he had a left hemiplegia which gradually cleared up completely. Whether the convulsive attacks were Jacksonian or general at that time is not known. However, they

Fig. 3.—Case 1.

Fig. 4.—Case 1.

have been general for the past several years. Shortly after the onset of the convulsions, roentgenograms of the skull were taken and were negative. Neurologists stated that there was no organic cause for the convulsive phenomena. No other pertinent history was elicited.

Physical examination showed the patient to be a well-nourished white male 5 feet 11 inches in height and weighing 169 pounds. Physical examination and neurologic examination were entirely negative for any pathology. No skin nevi were found.

Stereoroentgenograms of the skull revealed no evidence of any intracranial pathology.

Psychometric examination, Binet-Simon scale (Stanford revision) gave a mental age of 14-4; intelligence quotient, 89.

The author wishes to express his gratitude to Doctor V. M. Leffingwell and Doctor C. C. Marshall of Sharon, Pennsylvania, for their courtesy in permitting him to present this next case.

CASE 2.—L. H., a white female, aged four years, was admitted to the C. H. Buhl Hospital because of severe convulsive phenomena and paralysis of the right arm and leg. The following history was obtained. At birth the child had a port-wine nevus on the left side of her face. This had been partially removed by the application of radium and scars of radium burns were present over the left temporal region and the left malar bone. The child had always been bright and active and normal in her mental reactions. During a three-month period before her admission to the hospital the child would occasionally come in from play holding her hand over the left side of her head and go to bed complaining of a headache. About two weeks prior to admission to the hospital the child began having twitchings of the right side of the body which became typical Jacksonian convulsive phenomena. These persisted for several days and were associated with a temperature of 101° F. On admission to the hospital the patient was in a state simulating status epilepticus. There was a definite spastic hemiplegia of the right side of the body. The patient's general condition was not good.

Family history revealed that a maternal aunt was subject to epileptic attacks. Otherwise the family history was negative.

On admission a spinal tap was performed immediately. It revealed a slight increase in pressure measured by a mercury manometer. The fluid was clear. Sugar and albumin readings were within normal limits. There were no red blood cells present microscopically nor evidence of old hemorrhage. The cell count was normal.

A diagnosis of intracranial hemangioma on the left side was made and immediate operation advised.

Under ether anesthesia a button of bone about the size of a silver dollar was removed from over the left temporal region. The brain surface and meninges showed a remarkable increase in vascularity. No area of hemorrhage or vessel rupture could be located on the brain surface. A needle on a syringe was then inserted into the temporal lobe for a depth of about one and one-quarter inches. It was directed somewhat forward and downward. About 10 c.c. of bloody fluid was withdrawn. No other procedure was attempted and the wound was closed without drainage.

Convalescence was uneventful. The hemiplegia disappeared in about one month. The patient occasionally complained of headache during this period. This was always mild. At the present time, almost a year after operation, the patient leads a normal life, is bright mentally and active physically, and shows no residuals. There have been no further convulsive phenomena.

On inserting a needle into juvenile brains at autopsies in the area and manner described by Doctors Leffingwell and Marshall we found that, almost invariably, the needle entered the inferior horn of the lateral ventricle. We feel that in all probability the fluid withdrawn at operation was from this ventricle. The fluid definitely was not all blood. It may have been spinal fluid from the ventricle mixed with fresh blood produced by the insertion of the needle. The absence of blood in the original spinal tap would bear out this premise.

COMMENT

A review of the literature on this subject reveals that recent authors are practically unanimous in the belief that the facial nevus and associated intracranical hemangioma are developmental anomalies. However, there is some disagreement in the origin of the anomaly. Cushing

and Bailey,[5] among others, believe that the vascular anomalies are primarily of mesodermal origin. Yakovlev and Guthrie, on the other hand, believe that while histologically and histogenetically they appear to be anomalies of mesodermal origin, they are, from a pathogenic standpoint, of ectodermal origin. These authors advance considerable data to prove this contention, for upon it they build their hypothesis that the mental defect and the epilepsy are part of the faulty embryogenesis which produces the vascular anomaly. In this respect they call attention to two other syndromes in which epilepsy and mental phenomena are associated with cutaneous lesions, namely, Bourneville's tuberous sclerosis and Recklinghausen's neurofibromatosis, and group the three syndromes under the term congenital ectodermatoses. They arrive at the conclusion that the mental retardation and epilepsy are not secondary manifestations but concomitant manifestations of faulty embryogenesis, i.e., "that the vascular anomaly is only more conspicuous part of the malformation which affects the cerebrum as a whole . . . that the developmental factor is more important in the causation of the epilepsy than the subsequent lesion, be it congenital or acquired, vascular or of any other nature." This contention, of course, follows the belief of some authors, that birth injury seldom produces mental defect unless a familial tendency to faulty germ plasm exists. It is a broad statement, and fails to take into consideration many anatomic, physiologic, and clinical facts.

It is well known that any lesion within the skull is capable of producing convulsive phenomena whether a predisposition exists or not. Any lesion which destroys nerve cells is capable of producing mental deficiency, mental deterioration, or psychic changes. It is also true that among mental defectives of the primary type anomalies of development are more common than among the general population. Epilepsy is likewise more common among mental defectives of the primary type than among those with no familial history of faulty germ plasm. And epilepsy itself whether idiopathic or symptomatic is capable of producing, and often does produce, mental deterioration; often of a marked degree. It is the author's belief that whereas the question of ectodermal or mesodermal origin of the anomaly in question is important from an embryologic viewpoint, the answer to the question will neither prove nor disprove an embryogenetic relationship of the vascular anomaly to the mental retardation and epilepsy.

Assuming that the neuromerically associated cerebral and cutaneous lesions are of ectodermal origin, which from Yakovlev and Guthrie's researches is quite probable, there is no clinical proof that the motor and psychic phenomena are primarily a part of the picture. In Recklinghausen's disease mental retardation is by no means a constant finding. In two of the four cases reported by Yakovlev and Guthrie it was not demonstrated. In the two cases in which it was demonstrated, one gave

a positive history of germ plasm defect and in the other no history was mentioned. In the two cases which showed no mental deficiency epilepsy did not occur until the ages of forty and fifty-two at which time it could have been the result of gliosis or some entirely unrelated condition.

In Bourneville's tuberous sclerosis there is an actual loss of nerve cells of the cortex and the presence of large plaques of sclerotic tissue within the cerebral cortex. The actual loss of nerve cells could well be responsible for the mental deficiency which is usually of a profound degree and commensurate with the pathologic picture.

In the series of cases of facial nevi associated with intracranial vascular anomaly reviewed by Greenwald and Koota it can be seen that in many of the cases that came to autopsy or operation there was present an actual destruction or loss of nerve cells from the cerebral cortex. In many instances there was a deposition of lime salts within the cortex. This destruction was sufficient to account for the mental changes noted in the cases reported. The presence of the vascular lesion within the skull, with its tumor-like morphology, would be just as capable of producing convulsive phenomena as would any brain tumor. Likewise, it is important to note, that many of the convulsions were Jacksonian in type early and later became general, as in our cases. Jacksonian epilepsy is not the usual manifestation of an hereditary taint, but of some intracranial process as tumor, localized vascular accident, or pressure.

Tredgold believes that when amentia is associated with the presence of a facial nevus and an intracranial hemangioma that it is of the primary type, is merely an associated developmental anomaly, and is not a necessary consequence of the hemangioma. Stewart is of the same opinion. Cushing and Bailey[5] believe that the convulsive phenomena are the result of thrombosis or hemorrhage from the middle cerebral artery. None of these theories explain the mental phenomena satisfactorily when the cases reported have been analyzed from a clinical standpoint. Greenwald and Koota found mental changes in 60.9 per cent of cases reported. They found also that rarely did the mental changes stand in the foreground. "In most reported cases the children were simply mentally retarded and showed only impairment of speech or one or more of the following: faulty memory, bad judgment, failure of comprehension, inability to fix the attention. In many instances the child showed a mental age that was only slightly behind the actual age. It should be emphasized, however, that occasionally cases are encountered without mental changes." In fact 39.1 per cent showed no mental changes. In brief, the outstanding mental symptoms heretofore reported as occurring in this syndrome are those associated with any intracranial pathology, particularly with brain tumor, and are not syndrome specific. The eye findings recorded were likewise those that might be found in any condition producing increased intracranial pressure.

More interesting data are uncovered when we check the degree of mental defect with the age of the patient at time of death or operation in 17 cases on which this data are available. There were six patients who showed a normal mentality. Two of these were four years of age, two were five years, one was ten years, and one was forty-five years. Four patients showed mental deterioration (not retardation) and all were adults. Two showed slight mental retardation and were adults. Six exhibited profound mental retardation and all but one of these were over twelve years of age. In general those cases with the more profound mental defect evidenced the most damage by the angioma to the brain substance itself.

These figures would seem to indicate that the degree of mental defect depends upon the extent of the lesion and the duration of the symptoms. The duration of the symptoms is of the utmost importance when we recall the profound deteriorating effects convulsive phenomena often have on psychic function. In many cases an epileptic of normal mentality at three or four years will have deteriorated to a low-grade idiot by puberty. Case 1 of the cases herein reported shows how deterioration can occur. Case 2 is further evidence that the syndrome can exist in the presence of a normal mentality. Primary mental deficiency shows a defect of neurons at birth and from then onward through life. Case 1 of this series exhibits a rather profound germ plasm defect. The mental deficiency is in all probability primary but increased by the presence of the extensive intracranial hemangioma.

Another factor which must be considered is the side on which the hemangioma occurs. An hemangioma on the left side in a right-handed person is conceivably capable of producting more mental changes than if it were on the right side. This is offered merely as a suggestion for future study.

SUMMARY

The author is of the opinion that in the majority of cases of facial nevi associated with intracranial hemangioma the motor and psychic phenomena observed are secondary to the intracranial hemangioma and that they are due to the same factors which will produce motor and psychic phenomena in instances in which other intracranial tumors can be demonstrated or other factors which will produce destruction or faulty function of brain cells. He is also of the opinion that in many cases, but not in the majority of cases, a concomitant primary mental deficiency may exist which will add to the severity of the objective mental responses. The rather high percentage of cases in which primary mental deficiency may coexist is probably due to the fact that developmental anomalies are more frequent among primary aments than among those with a normal mentality. The author offers in support of the above statements the following well-established clinical facts:

(1) Any intracranial tumor or tumor-like process is capable of producing convulsive phenomena, frequently Jacksonian in type. In the cases reported in the literature of the syndrome under discussion most cases began with Jacksonian attacks and later became general or remained Jacksonian. (2) Jacksonian epilepsy is not the usual type of convulsive phenomena associated with a germ plasm defect responsible for convulsive disorders. (3) Any convulsive disorder persisting over a period of years is capable of producing mental deterioration. In the cases reported in the literature in which mental changes were noted the average age of the patient at time of death was greater than of those with normal intelligence. (4) Mental retardation as a result of primary amentia is exhibited early in life.

It is conceded that Yakovlev and Guthrie were correct in classifying the phenomena of a facial nevus associated with an intracranial hemangioma with two other syndromes which present neurocutaneous manifestations and in grouping the three under the term "congenital ectodermatoses." But we do not believe that in the first mentioned of the three syndromes the concomitant mental changes or epilepsy are embryogenetically associated, but are the result of destruction of anatomic and physiologic units within the brain. This is important from a prognostic standpoint since cases cured by operation or by radium, and by a combination of the two, have been reported.

CONCLUSIONS

1. That in the syndrome characterized by the presence of a facial nevus and an intracranial hemangioma, the other symptoms, i.e., convulsive phenomena, hemiplegia, mental changes, and eye findings are secondary to the presence of the hemangioma within the skull.

2. That in some cases a primary mental deficiency may coexist which will tend to intensify the mental symptoms.

NOTE: The roentgenographic studies and photographs were made by H. C. Eaton, M.D.

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A COMPARATIVE STUDY OF THE LEVINSON AND TRYPTOPHAN TESTS AS AIDS IN THE DIAGNOSIS OF TUBERCULOUS MENINGITIS

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OF THE various laboratory tests proposed, either to establish or to exclude a diagnosis of tuberculous meningitis, the tryptophan test of Furth and Nobel, and the Levinson or mercuric chloride-sulphosalicylic acid test have been most widely investigated.

In a review of the literature, Aiello[1] concluded that the tryptophan reaction was positive in about 90 per cent of the cases of tuberculous meningitis; that there were about 2 per cent false positive reactions, and that a negative tryptophan test usually ruled out a diagnosis of tuberculous meningitis. Aiello also showed that a positive tryptophan test occurred independently of the protein content of the spinal fluid. More recently, Lichtenberg[2] showed that in his 25 cases of tuberculous meningitis, the tryptophan test was positive in all. Contrariwise he showed that spinal fluids which yielded negative tryptophan reactions were from patients with nontuberculous lesions. He found that purulent, xanthochromic and hemorrhagic spinal fluids gave false positive reactions. Age and bacterial contamination did not alter the reactions.

Tashiro and Levinson[3] in 1917 were first to establish the fact that the alkaloidal and metallic precipitation of cerebrospinal fluid could be used as a diagnostic aid in various meningitic processes. Since then the mercuric chloride-sulphosalicylic acid, or Levinson test, has been given clinical application by various workers. Levinson[4] himself used the test in many cases and concluded that it could be used as an aid in the diagnosis of tuberculous and nontuberculous lesions of the central nervous system. Pons and Fletcher[5] found the test positive in about 95 per cent of 20 cases of tuberculous meningitis. The work of Peterman[6] seems equally encouraging. Giordano and Ableson[7] reported a study of the Levinson test on 98 spinal fluids, 23 from 17 proved cases of tuberculous meningitis. In the 98 spinal fluids examined, 32 per cent yielded false reactions. In 90 per cent of the proved cases of tuberculous meningitis, the Levinson test gave the characteristic ratio. Messeloff's experience[8] with the test has been more encouraging. He examined 22 spinal fluids from 17 patients. Six of the cases had proved tuberculous meningitis. In all of the six cases, the Levinson test gave

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the characteristic ratio. In every instance where the reactions were found to be negative, the disease was nontuberculous.

METHODS

The tryptophan test is a color reaction said to depend on the presence of the tryptophan groups.

Two to 3 c.c. of the spinal fluid were placed in a 30 c.c. test tube, 15 mm. in diameter. To the spinal fluid was added 15 to 18 c.c. of concentrated hydrochloric acid and 2 to 3 drops of 2 per cent formaldehyde solution. The contents were shaken and allowed to stand from four to five minutes. The solution was then layered with about 1 to 2 c.c. of 0.06 per cent sodium nitrite solution and allowed to stand from two to three minutes. At the junction of the two liquids a delicate violet ring formed when the reaction was positive, and a brown ring or no ring when it was negative. In doubtful reactions the test was considered negative. All fluids were examined immediately after withdrawal.

For the principles underlying the Levinson or mercuric chloride-sulphosalicylic acid test and the influence of associated factors, the publications of Levinson,[4, 9] of Tashiro and Levinson,[3] of Giordano and Ableson[7] may be referred to. The test appears to be based on variations of the H-ion concentration in the cerebrospinal fluid. Fluids from cases of tuberculous meningitis, if examined immediately after withdrawal from the body have a pH of from 7.4 to 7.6. A similar value is obtained from normal fluids. However, the pH of fluids obtained from cases of meningococcic meningitis have an average of 7.3. The difference in the pH of the cerebrospinal fluid is sufficiently marked to show the presence of the differently charged proteins in the two pathologic conditions by adding suitable precipitants to the fluid. Tashiro and Levinson[3] selected a 1 per cent solution of mercuric chloride as the metallic precipitant and a 3 per cent sulphosalicylic acid solution as the alkaloidal precipitant. They found that in tuberculous meningitis, the precipitate in the mercuric chloride tube, if measured in millimeters was 2 to 3 times the amount in the sulphosalicylic acid tube. The converse was found in meningococcic meningitis, the sulphosalicylic acid precipitate measuring 2 to 3 times that of the mercuric chloride. It was later discovered that by the use of a 2 per cent solution of mercuric chloride more reliable results could be obtained. Messeloff[8] suggests that the test should not be considered positive for tuberculous meningitis unless the precipitate in the mercuric chloride tube is more than 5 mm. The test is to be considered negative if the mercuric chloride sediment is less than 5 mm., regardless of what ratio it bears to the sulphosalicylic acid precipitate.

One-half to 1 c.c. of spinal fluid was placed in each of two narrow, flat-bottomed test tubes. An equal amount of 2 per cent mercuric chloride was added to one and 3 per cent sulphosalicylic acid to the other. The tubes were tightly stoppered, sealed with melted paraffin, shaken and placed in a rack at room temperature. After an interval of twelve to twenty hours, the tubes were again shaken in order to dislodge any precipitate that might have adhered to the sides. The final readings were usually made after twenty-four hours and in a few cases not until forty-eight hours. The fluid was examined immediately after withdrawal. The test was considered positive when the ratio of the sediment in the mercuric chloride tube to the sediment in the sulphosalicylic acid tube was as 2:1 or 3:1.

RESULTS

The present communication is a report of results obtained with the Levinson and tryptophan tests of the spinal fluids of 35 patients who

TABLE I

CASES OF TUBERCULOUS MENINGITIS

NO.	CASE	SUGAR	CHLORIDES	PROTEIN	TOTAL NO. CELLS	PER CENT POLYS.	PER CENT MONO.	LEVINSON		TRYPTOPHAN
								MERCURIC CHLORIDE	SULPHO-SALICYLIC ACID	
1	A. S.	28	626	80	82	5	95	5.0 mm.	0.5 mm.	Negative
		45	632	80	–	–	–	4.5 mm.	0.5 mm.	Positive
		50	638	85	–	–	–	4.0 mm.	0.3 mm.	Positive
2	D. C.	28	611	100	400	4	96	14.0 mm.	4.0 mm.	Negative
		25	642	82	423	6	94	12.0 mm.	3.0 mm.	Negative
3	M. S.	45	621	–	400	10	90	–	–	Negative
4	H. S.	27	633	112	170	4	96	15.0 mm.	3.0 mm.	Negative
		28.5	602	94	353	0	100	12.0 mm.	2.0 mm.	Negative
		30	625	80	130	0	100	8.0 mm.	2.0 mm.	Negative
		31	627	80	247	0	100	7.0 mm.	2.0 mm.	Negative
5	W. T.	17	542	43	170	2	98	5.0 mm.	6.0 mm.	Negative
		18	573	–	193	2	98	6.0 mm.	2.0 mm.	Negative
6	A. R.	44	607	–	90	8	92	–	–	Negative
		–	605	–	112	5	95	15.0 mm.	4.0 mm.	Negative
		77	605	–	200	12	88	–	–	Negative
7	L. S.	40	588	–	250	0	100	13.5 mm.	4.5 mm.	Negative
8	F. H.	45	605	82	320	0	100	6.0 mm.	2.0 mm.	Negative
		23	630	60	200	0	100	7.0 mm.	3.0 mm.	Negative
		39.2	620	90	–	–	–	12.0 mm.	3.0 mm.	Negative
		40	623	80	–	–	–	6.0 mm.	2.0 mm.	Negative
9	L. D. A.	20	600	172	–	–	–	13.0 mm.	6.0 mm.	Positive
10	A. B.	10	647	125	90	5	95	13.0 mm.	4.0 mm.	Positive
		10	610	130	94	2	98	12.0 mm.	3.0 mm.	Negative
		17	660	128	125	2	98	14.0 mm.	4.0 mm.	Negative
		26	643	135	96	10	90	15.0 mm.	4.0 mm.	Positive
		26	620	112	422	4	96	15.0 mm.	3.0 mm.	Positive
		19	613	175	76	2	98	16.0 mm.	3.0 mm.	Positive

TABLE II

CASES OF NONTUBERCULOUS INVOLVEMENT

NO.	CASE	SUGAR	CHLORIDES	PROTEIN	TOTAL NO. CELLS	PER CENT POLYS.	PER CENT MONO.	LEVINSON		TRYPTOPHAN	DIAGNOSIS
								MERCURIC CHLORIDE	SULPHO-SALICYLIC ACID		
1	R. L.	0	719	–	123	25	75	3.0 mm.	3.5 mm.	Negative	Influenzal meningitis
2	E. F.	73	702	40	–	–	–	4.0 mm.	4.0 mm.	Negative	Brain tumor
3	H. G.	105	665	38	65	0	100	3.0 mm.	3.0 mm.	Negative	Anterior poliomyelitis
		125	650	30	–	–	–	2.0 mm.	2.0 mm.	Negative	
4	L. D.	54	649	50	–	–	–	–	–	Negative	Streptococcus meningitis
		20	600	172	850	95	5	13.0 mm.	6.0 mm.	Positive	
		20	580	233	6600	95	5	–	–	Positive	
5	H. S.	86	743	60	19	20	80	9.0 mm.	3.0 mm.	Negative	Encephalitis
		78	738	72	10	0	100	9.0 mm.	3.0 mm.	Negative	
6	L. W.	55	742	22	2	–	–	3.0 mm.	1.0 mm.	Negative	Habit spasm
7	S. Z.	60	635	30	10	0	100	2.0 mm.	2.0 mm.	Negative	Meningismus
8	G. T.	90	632	20	12	0	100	2.0 mm.	1.0 mm.	Negative	Meningismus
9	V. O.	72	645	140	3087	53	47	12.0 mm.	5.0 mm.	Negative	Streptococcus meningitis
10	R. M.	0	631	–	1300	85	15	7.0 mm.	5.0 mm.	Negative	Streptococcus meningitis
11	J. G.	65	670	–	0	0	0	0.4 mm.	0.4 mm.	Negative	Grand mal
12	A. B.	–	670	–	1400	88	12	5.0 mm.	3.0 mm.	Negative	Pneumococcus meningitis
13	R. T.	59	724	–	400	25	75	2.0 mm.	2.0 mm.	Negative	Encephalitis

TABLE II—CONT'D

NO.	CASE	SUGAR	CHLORIDES	PROTEIN	TOTAL NO. CELLS	PER CENT POLYS.	PER CENT MONO.	LEVINSON		TRYPTOPHAN	DIAGNOSIS
								MERCURIC CHLORIDE	SULPHO-SALICYLIC ACID		
14	R. L.	–	588	–	550	96	4	5.0 mm.	5.0 mm.	Negative	Streptococcus meningitis
15	W. P.	50	640	–	488	33	67	6.5 mm.	2.5 mm.	Negative	Encephalitis
		–	–	–	–	–	–	7.0 mm.	4.0 mm.	Negative	
16	A. G.	64	662	–	2	0	0	4.5 mm.	4.0 mm.	Negative	Petit mal
17	A. F.	60	669	170	6000	95	5	14.0 mm.	14.0 mm.	Positive	Brain abscess
		67	696	142	2692	95	5	10.0 mm.	7.0 mm.	Positive	
		52	690	104	360	–	–	9.0 mm.	6.0 mm.	Negative	
		59	702	84	295	–	–	8.0 mm.	6.0 mm.	Negative	
18	J. S.	55	630	–	–	–	–	1.5 mm.	1.5 mm.	Negative	Quadriplegia?
19	S. H.	–	–	–	1150	86	14	7.0 mm.	12.0 mm.	Negative	Streptococcus meningitis
20	V. T.	16	628	–	200	90	10	5.0 mm.	3.0 mm.	Negative	Streptococcus meningitis
		27	636	–	330	96	4	6.0 mm.	4.0 mm.	Negative	
21	G. G.	12	624	147	3000	90	10	3.0 mm.	5.0 mm.	Negative	Staphylococcus meningitis
22	C. E.	42	–	–	–	–	–	–	–	Negative	Encephalitis
23	D. S.	70	702	20	0	–	–	1.0 mm.	1.0 mm.	Negative	Birth injury (hemiplegia)
24	F. S.	15	664	90	4800	90	10	2.0 mm.	2.0 mm.	Negative	Influenzal meningitis
25	K. S.	38	683	250	3200	85	15	2.0 mm.	9.0 mm.	Negative	Meningococcus meningitis
		50	694	85	3800	85	15			Negative	

had various types of central nervous system involvement while in the Long Island College Hospital.

Of the 35 cases there were 10 cases of tuberculous meningitis. Only those cases were considered to have tuberculous meningeal involvement in whom the tubercle bacilli were demonstrated in the spinal fluid or presented positive postmortem findings.

The tests were applied immediately after withdrawal of the fluid from the body. In most of the cases the tests were performed repeatedly on fluid removed on different occasions from the same patient. Examination of fluids removed after the administration of therapeutic sera or fluids which appeared contaminated with blood are not included.

In all, 62 spinal fluids were examined. Twenty-seven of the 62 spinal fluids were from the 10 proved cases of tuberculous meningitis; 35 of the 62 spinal fluids were from 25 cases who had various meningeal or central nervous system involvement of nontuberculous character.

The Levinson test was positive in 100 per cent of the cases of tuberculous meningitis. The test gave the characteristic ratio in 4 cases of 24 cases of nontuberculous involvement of the central nervous system.

The tryptophan test was positive in only 3 of the 10 proved cases of tuberculous meningitis, and not consistently so. The test was positive in 2 cases of the 25 cases of nontuberculous involvement of the central nervous system. Both cases presented purulent fluid. It must be stated that the tryptophan test was not consistently positive in purulent fluids. There seemed to be no relationship between the polymorphonuclear content of the fluid and a false positive reaction.

The tryptophan and Levinson tests were both positive in Case 4; one of streptococcus meningitis.

An attempt was also made to study the relationship of the Levinson and tryptophan tests to the sugar, chloride* and protein contents as well as to the white blood cell study of the fluid.

SUMMARY

The Levinson test was positive in 100 per cent of the cases of tuberculous meningitis. The tryptophan test was positive in 30 per cent of the cases of tuberculous meningitis.

The Levinson test was positive in 16 per cent of the cases of nontuberculous involvement. The tryptophan test was positive in 8 per cent of the cases, both cases presenting a purulent fluid.

There was no significant relationship between the reactions of the Levinson and tryptophan tests and the sugar, chloride, protein contents and white blood cell study of the spinal fluids.

*Chloride determination of the spinal fluid was done according to the method of Van Slyke and Sendroy, J. Biol. Chem. 58: 523, 1923. Normal range for children is 600 to 700 mg. 100 c.c.

CONCLUSIONS

The Levinson and tryptophan tests are not without discrepancies and should not be considered important aids to the present routine methods of making or ruling out a diagnosis of tuberculous meningitis.

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LYMPHOGRANULOMA VENEREUM* IN CHILDHOOD

Review of the Literature With Report of a Case

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SINCE the early description of lymphogranuloma venereum by Durand, Nicolas, and Favre,[1] much has been learned and added to the knowledge of the "sixth venereal disease." Thousands of cases in adults have been described and extensive studies have been carried out, the most important of which are those of Hellerstrom[3] and Stannus.[2] It is noteworthy, however, that little is known concerning the disease in childhood, and it is generally assumed to be exceedingly rare during this period of life. This fact is readily evident from reports in which large numbers of cases have been described. Thus, in Von Hamm and Lichtenstein's series[4] of 154 cases none were under fourteen years of age; and in Kornblith's group[5] of 30 cases none were under sixteen years of age. In Bacon's group[6] of 155 cases the youngest was fourteen years; and in Hellerstrom's series[3] of 47 cases all were adults. De Wolf and Van Cleve,[7] in their careful analysis of 58 cases, go so far as to state that lymphogranuloma venereum is "not seen in childhood."

That the actual incidence of lymphogranuloma venereum in childhood is unknown at the present time seems probable in view of the lack of attention it has received in the literature and the consequent unfamiliarity of pediatrists with its manifestations.

Up to the present time, there has been but a single case reported in English in the pediatric literature. Other isolated descriptions have appeared in recent years, but have attracted comparatively little attention. It is the purpose of this paper to evaluate critically the available data concerning these cases, nine in all, and to include observations on one additional case.

CASE REPORT

S. W., a six-year-old colored girl, was first seen in the clinic on Aug. 4, 1936, at which time she complained of swelling in both inguinal regions of ten days' duration. The family history revealed that both parents had contracted syphilis about a year previous and both had been treated for several months. In addition, the mother had had a vaginal discharge for several years.

The past history of the patient was quite irrelevant to the present illness. There had been no symptoms suggestive of congenital syphilis. She had been vaccinated and had received prophylactic injections against diphtheria. She had had measles, varicella, and mumps in early infancy.

*Recently adopted by the American Medical Association for lymphogranuloma inguinale.

From the out-patient clinic of the Department of Pediatrics, The Jewish Hospital of Brooklyn, Dr. Benjamin Kramer, pediatrician-in-chief.

Ten days prior to her admission to the out-patient department, painful swellings appeared in both groins. They progressed in size until, at the time of the first examination each inguinal area contained a mass about 3 inches long by ¾ inch in diameter and cylindrical in shape. These appeared to be inguinal lymphatic glands. There was no fever or evidence of recent infection or injury. There was a scanty, whitish, foul-smelling discharge from the vagina and some inflammation of the urethra. No lesions were found in the vaginal orifice. The remainder of the examination revealed nothing unusual except for moderate undernutrition and a functional systolic murmur at the apex; the temperature did not exceed 99.6 F°.

The Wassermann and Kline tests were negative. The first vaginal smear was suspicious of gonorrheal infection, but subsequent smears and complement fixation tests were negative. Cultures and stained smears from fluid obtained by puncture of one of the enlarged glands failed to reveal any organisms. Tuberculin tests were negative up to 1 mg. Heterophilic agglutination tests were likewise negative. The blood showed 6,700 and 7,100 white blood cells on two occasions with eosinophilia of 6 per cent and 9 per cent respectively. The Frei test was negative on the first test and questionable on the second, but after four weeks it was definitely positive.

Fig. 1.—Lymphogranuloma venereum. Photograph of the patient taken fifteen weeks after onset showing residual bilateral inguinal adenitis.

The reaction consisted of a 7 mm. papule and 1.5 cm. zone of erythema. The test was performed with infected mouse-brain antigen, normal mouse-brain tissue being used as a control (see discussion of Frei test). The inguinal adenopathy continued to improve without any therapy. The fluctuation gradually subsided, and after fifteen weeks the inguinal glands became firm, indurated, mobile, nontender, and about one-third their original size (Fig. 1). The vaginal discharge disappeared within a few days after admission to the clinic, and left no local sequelae. Symptoms referable to the rectum were never present. The child remained quite well during the period of observation.

During the initial visits to the clinic the child was accompanied by her grandmother. When her parents were asked to appear for examination, it was discovered that both were being treated for syphilis in another clinic. Both were found to have markedly positive Frei tests as well as definite lesions of lymphogranuloma venereum. The mother had bilateral inguinal adenitis and vulval elephantiasis with an ulcerative lesion near the posterior fourchette (Fig. 2). She showed no abnormality of the rectum when examined proctoscopically. The father had bilateral inguinal adenitis and a partially healed penile sore (Fig. 3). The diagnosis of lymphogranuloma venereum had apparently not been made nor even suspected in the parents until the disease was discovered in the child.

OCCURRENCE

It is interesting that 7 of the 9 juvenile cases have been reported since 1932, and of these, 4 were described in the last two years. This apparent increase in juvenile cases is undoubtedly due to more widespread recognition that this disease may occur in childhood rather than to actual increase in the incidence of the disease. In 1932, Chevallier, Moricard, and Bernard[11] predicted ". . . that similar cases would not be exceptional if tests for Nicolas-Favre disease were made in hospitals for children." The case herein described undoubtedly would have been missed had it not been suspected and a Frei test performed and *repeated*, since the course was not typical. Indeed most of the cases in children were not classical examples of the disease and were discovered because of suspicious symptoms. Although it may not be advisable to do routine Frei tests in children's hospitals and clinics, lymphogranuloma venereum should be considered in children presenting vague rectal or genitourinary symptoms or inguinal adenopathy. (Cervical and axillary adenitis due to lymphogranuloma venereum have also been reported.)

CLINICAL MANIFESTATIONS

Of the 10 collected cases in children, 9 were in females and one in a male. The latter case is a doubtful one. The youngest patient in the series was two weeks old; the next was three years; and the remainder were between six and fourteen years of age. There were 2 colored children, 7 white, and 1 Porto Rican. In 7 of the cases the source of infection was traced to another member of the family. In one patient (Case VI), a common enema tip was apparently the carrier of the infection; in the others, there had been close contact with persons proved to have the disease. In none was there a history of sexual contact. This and the fact that cervical and axillary adenopathy follows mouth and hand lesions[3, 12, 2] indicate that sexual intercourse is not the only method of transmission of lymphogranuloma venereum.

The disease is caused by a virus which enters through a small and usually evanescent lesion or abrasion on the penis in males, and within the vagina in females. Most observers fail to discover the primary lesion, but some, especially Dalton,[16] found it in over one-half of the patients. In none of the childhood cases was the primary lesion described. Lymphogranuloma venereum can, however, develop in connection with an apparent urethritis which is accompanied by slight pain and by the presence of small polycyclic ulcerations on the urethral orifice. It is distinguished from gonorrheal urethritis by the absence of gonococci as described by several observers, notably Phylactos,[17] Spillmann,[18] Gamna,[19] and Capelli.[20] Kornblith[5] further describes the discharge as loose,

Fig. 2.—Lymphogranuloma venereum. Vulval elephantiasis with an ulcerative lesion near the posterior fourchette in the patient's mother, who also demonstrated bilateral inguinal adenitis.

Fig. 3.—Lymphogranuloma venereum. Partially healed penile sore in patient's father, also accompanied by bilateral inguinal adenitis.

TABLE I

ANALYSIS OF PREVIOUSLY REPORTED CHILDHOOD CASES

AUTHOR YEAR	AGE	SEX	RACE	SOURCE	HISTORY	PHYSICAL FINDINGS	LABORATORY FINDINGS	FREI TEST	COURSE AND THERAPY	REMARKS
Case I Weiss and Cain[8] 1925	14	F	W	Not discovered.	Swelling and pain in left inguinal region which progressed rapidly.	Fever, pain in inguinal region with spontaneous discharge of greenish pus in a day or two.	Typical of acute infection. Nonspecific.	Had not yet been introduced.	Rapidly progressive to suppuration after onset, then healing and recurrence of suppuration twice. Finally a large abscess in the iliac fossa was incised and drained through the first with subsequent complete healing.	Histologically the glands which were expelled by the suppurative discharge were reported as "probable Nicolas-Favre."
Case II Chevallier and Bernard[9] 1930	14	M	W	No sexual contact.						Except for the fact that there had apparently been no sexual contact, details are omitted in this case, both in the original report and in its quotation by Stannus[2] as an authentic case in a child. Frei test is not mentioned.

TABLE I—CONT'D

Case III Lujan and Rotter[10] 1932	6	F	W	No sexual contact, probably direct contact. See Case IV.	Insidiously 14 days previous with gradually increasing swelling.	Inguinal adenitis—bilateral; overlying skin slightly red.	None reported.	4 plus.	Later course not described; apparently cured by surgical excision.	Histologically the lesions were typical.
Case IV Lujan and Rotter[10] 1932	7 (sister of above)	F	W	Mother had positive Frei test, no clinical signs of disease. Sister had some buboes some time previously. Cousin of mother had been operated on for inguinal buboes. Two other cousins with buboes often slept with children. No sexual contacts, probably direct contact.	Sudden fever, headache, general symptomatic reaction, and enlargement and tenderness of the inguinal nodes.	Bilateral inguinal adenopathy to size of dove's eggs. Overlying skin normal.	None reported.	4 plus.	Electrargol was used locally and swelling disappeared in ten days.	
Case V Chevallier, Moricard, and Bernard[11] 1932	3	F	W	Not discovered.	Suppuration of left inguinal region and left labium beginning at 14 months of age.	Oval and large ulceration in left groin, base uneven, red and moist. Another in the inguinovulval fold. Glands palpable on both sides; not adherent to skin.	Tuberculin test negative.	4 plus; not performed until one month after healing.	Iodine ointment, incision and drainage, ultraviolet therapy. Tuberculous "allergine" injections were given with some improvement, alternating with recurrence of disease for sixteen months. Then complete healing with cicatrization.	Nonpathogenic staphylococcus cultured from discharge (probably secondary invader).

TABLE I—CONT'D

AUTHOR YEAR	AGE	SEX	RACE	SOURCE	HISTORY	PHYSICAL FINDINGS	LABORATORY FINDINGS	FREI TEST	COURSE AND THERAPY	REMARKS
Case VI Elitzak and Kornblith[12] 1935	8	F	Porto Rican	Definite cases in parents. Mother and child used common enema tip. No abnormal sexual contacts.	At three years child had nonspecific vaginitis, was well until eight years of age when melena, visible in every bowel movement was noted. Disappeared in one week.	Few small glands in axillary and inguinal regions. Hymen intact. No vaginal lesion or discharge. Proctoscopic: several ulcerations 5 cm. up.	Eosinophilia 9 per cent.	4 plus.	Frei antigen in increasing doses to establish immunization. Healing of primary lesions after this series. Recurrence two months later with persistence.	Typical adult rectal course. Was infection congenital? Unlikely start at three years with vaginitis. Acquired by contact at eight years.
Case VII* Dummer and Tamura[13] 1935	10	F	C	An uncle had swollen inguinal glands 5 yr. previously. Mother and male roomer showed strongly positive Frei reactions. No history of sexual indiscretion was obtained.	Pain in both inguinal regions eight days' duration before admission to hospital. Marked inguinal swelling becoming worse. Fever. There was evidence that there had been a vaginal discharge some time before onset.	Fever 102.4° F. Inguinal glands bilaterally enlarged 7 to 8 c.mm. in diameter. Tumor hot, indurated, extremely tender. Vagina, rectum, negative.	Within normal limits but for one positive vaginal smear which showed gram-diplococci.	Negative until seventeen days after onset after which it became strongly positive.	Glands became fluctuant and were aspirated several times before vaccine therapy was begun (126 days after onset) and twice after it was begun. Discharge much improved two weeks later with only slight induration remaining.	

*Also reported by J. T. Tamura in Northwest Med. 36: 39-41, 1937.

TABLE I—CONT'D

Case VIII Dick[14] 1936	2 wk.	F	W	Mother and father had proved cases of lymphogranuloma venereum.	Normal child born at term.	Normal infant.	Not reported.	4 plus.		Frei test done at five months of age 4 plus, indicating that positive reaction was not simply an allergic reaction transmitted from mother.
Case IX Dick[14] 1936	14	F	W	Mother had lymphogranuloma venereum for many years with rectal syndrome in 1906. Surgical extirpation followed by peritonitis and death.	Patient fourteen yr. of age in 1913 with stricture of rectum, which was surgically extirpated with recovery.			4 plus.		Author recalls this case in citation of above as to possibility of intrauterine route of infection.
Case X Present report	6	F	C	Parents (see report).	Bilateral inguinal swelling ten days before admission to clinic.	Inguinal adenitis bilateral. Glands about 3 inches by ¾ inch; apparently several involved and matted together. Vaginal discharge whitish, foul smelling, not profuse; slight urethritis.	One vaginal smear suspicious of gonorrhea. Remaining smears negative. Eosinophilia 6 per cent; later 9 per cent. Otherwise normal.	Slight doubtful reaction for about 3 to 4 weeks then positive.	Spontaneous remission of the swelling which took place very slowly. It was not complete in four months but the child was always well clinically after the first few days.	Proctoscopic, negative. No specific treatment. Parents discovered to have disease after diagnosis was made in child.

watery, and rapidly regressive since it has usually disappeared at the end of 3 to 4 days. This discharge may easily be an evidence of the presence of the primary lesion within the urethra and its evanescent character may be the reason for its being overlooked so often.

In 3 of the childhood cases, there was a vaginal discharge at one time or another which was very much like that described above. This is a large proportion if one considers the mildness and the fleeting character of the discharge.

It has long been recognized that in (adult) females ". . . it is the exception for the inguinal adenopathy to become manifest. The lymph drainage from the clitoris and external vulva passes into the inguinal nodes, whereas the supply from the vaginal mucosa and especially from the posterior vaginal wall drains into the lymph nodes around the rectum, where there are three lymph plexuses extending up into the rectum."[12] Yet of the 9 female children, 6 showed inguinal adenopathy only, one had inguinal and rectal pathologic changes (Case VI), and only one (Case IX) had rectal stricture alone! The ninth was the case of the infant (VIII). It should be noted that in Case VI there had been an obvious cause for direct implantation of the virus into the rectum since an enema tip used by the mother was used for the child. Thus it can readily be surmised that at least several more of the cases may have had a vaginal discharge which was not observed and that the urethral route (and consequently the inguinal route) is the most likely in these cases of acquired lymphogranuloma venereum in female children.

TRANSMISSION

Until recently, direct contact was thought to be the only modus of transmission of the disease. Dick,[14] however, reported the case of an infant whose parents had the disease and who showed a positive Frei test at two weeks of age and again at five months, with no clinical symptoms of lymphogranuloma venereum. Although the positive test may have been a transmitted allergic reaction from the mother, this is unlikely, in view of the persistently positive skin test. In view of Von Hamm and D'Aunoy's[15] recent suggestion that the disease has general as well as local manifestations and since in Dick's case there was a persistently positive Frei test with no clinical manifestations of lymphogranuloma venereum, many new and interesting problems arise. Is a positive test in early infancy merely an indication of immune bodies transmitted through the placenta? If so will the Frei test become negative later on just as in those children with positive Wassermann tests who have acquired the immune bodies but who have not had syphilis? Or will the disease become manifest clinically at a later age?

PATHOLOGY

For the purpose of this paper little need be said concerning the pathology of the disease. According to Kornblith,[5] biopsy and histologic examination are the final criteria in diagnosis. He found it characteristic in 11 of 13 cases. Grossman[21] states that the usual pathologic picture is one of a chronic nonspecific inflammatory nature. But Talbot[22] notes a characteristic lesion cautioning however that examination must be made before secondary infection sets in. The essential pathologic finding is a microabscess lined by one or two layers of epithelioid cells in a palisade arrangement. Occasional giant cells occur, as well as certain masses of a substance taking a chromatin stain, the significance of which is not yet understood, but caseation and calcification do not occur. The primary lesion shows the same changes and so does the skin lesion of the positive Frei test.

Laboratory Findings.—The only change which has appeared frequently enough to warrant mention is eosinophilia. This appeared in two (VI and X) of the childhood cases. It should be noted, however, that only three of the remaining cases (I, V, VII) reported any laboratory findings at all.

Frei Test.—This is an intradermal test involving a local reaction to the pus from unopened buboes of known cases of lymphogranuloma venereum. It was reported first by Frei[23] in 1927 and has been found by many observers to be specific.[1, 2, 6]

Some controversy has arisen over the recent use of a prepared mouse-brain antigen which has added a new possibility for error according to Strauss and Howard.[24] They found that normal (noninfected) mouse-brain tissue undergoes changes on standing for short periods of time and gives a positive intradermal reaction after this alteration. In 21 of 48 injections into normal controls, the reactions were 6 mm. or more in diameter and indistinguishable from true Frei reactions. In another 17 of these 48, they were 4 to 5 mm. in diameter and easily mistakable for positive reactions. In patients suffering from lymphogranuloma venereum and tested with normal mouse-brain tissue, 15 per cent of the reactions were indistinguishable from, and 75 per cent easily mistakable for, positive Frei tests. In all the cases, human material (pus from actual cases), dried mouse-brain antigen not kept over one month, or fresh preparations were quite reliable.

On the other hand, Grace and Suskind[25] seem to disprove this quite definitely by their tests on a much larger series—50 cases of proved lymphogranuloma venereum and 128 control cases. A typical positive reaction resulted from every test with lymphogranulomatous mouse-brain tissue in positive subjects and in those the papule produced was never less than 7 mm. in diameter. In 75 per cent of the cases the lesion was from 7 to 10 mm. in diameter. Of the control reactions 88.6

per cent were 1 to 4 mm. in diameter, none as large as 7 mm. The difference was readily recognizable, but they still advocated using the normal tissue as control in any test.

Of great importance is the fact that the Frei test does not become positive for two to four weeks after infection. Thus the test must be repeated, or postponed for at least a month after primary infection, if a dependable result is to be obtained.[12, 13] The case herein added (X) was a good example of this, since the disease was observed from its very onset. Two Frei tests were negative in the first few weeks and it was not until the fourth week that a definite positive reaction could be demonstrated. Dummer and Tamura[13] had had a similar opportunity in observing their case (VII) from its onset.

COURSE AND PROGNOSIS

Lymphogranuloma venereum is generally described as a disease which ". . . shows little or no tendency to spontaneous healing."[12] However, there is more than presumptive evidence that many cases have improved or regressed spontaneously. The multiplicity and variety of therapeutic methods credited with cure speak eloquently for the fact that none of these played a significant rôle in promoting healing. Undoubtedly, surgical extirpation or drainage was of great aid at critical points in several of the childhood cases (I, III, V, VII, IX), yet Cases IV and X, which were given medical treatment only, seemed to show improvement, regressing spontaneously without surgical interference or subsequent breakdown of the glands. It is not unlikely that many such cases have occurred and have been missed because it was not suspected that this could occur in lymphogranuloma venereum.

Though the course is invariably chronic and prolonged, the ultimate prognosis seems good, since of the 10 cases, 6 are clinically well (except for surgical scars), one required major surgical intervention with cure (IX), two more give no record of the outcome (II and VI) and the tenth is the infant (VIII).

TREATMENT

The therapy usually advocated is radical and complete extirpation with subsequent x-ray or quartz-lamp therapy. Kornblith[5] attempted desensitization with increasing doses of antigen starting with 0.1 c.c., the highest dilution used being 1-400. Twelve injections were given. The results were fairly good for relief of pain. Many discharging lesions began to heal after institution of this form of therapy. Antimony, tartar emetic, and various other therapeutic methods have been of doubtful value.

Caution in evaluating any of these modes of treatment is advocated by Hellerstrom.[3] Quoting Frei[26, 27] and Ramel,[28] he warns: "As . . . it

seems probable that the disease has a considerably greater tendency to spontaneous healing than was formerly supposed, one is compelled to exercise great prudence in judging the result of treatment." The present case (X) bears this out very strongly.

SUMMARY

The cases of lymphogranuloma venereum in children have been reviewed.

An additional case is reported in which the Frei test was positive after the latent period of four weeks and in which the clinical manifestations regressed spontaneously.

A characteristic early transitory vaginal discharge with urethritis accompanied by inguinal adenitis should cause one to suspect the diagnosis of lymphogranuloma venereum.

The significance of the specific Frei test was discussed.

Invaluable aid was rendered by Miss Charlotte Ross of the Social Service Department.

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DRUGS TRANSMITTED THROUGH BREAST MILK

PART I: LAXATIVES

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A STUDY of drugs administered to nursing mothers in respect to their elimination through breast milk is one of interest and importance not only to pediatricians but also to clinicians, obstetricians, nurses, mothers, and all individuals interested in child welfare. The interne can no longer afford to evade the query which is often asked by anxious lactating mothers, "Will the medicine I take affect the baby?" He must answer in either the affirmative or the negative.

In reviewing the literature dealing with this subject, there is little in the way of clinical investigation that has been carried on in this field. When one considers the rapid strides made in other branches of medicine, it is surprising that the study of foods and drugs which may be eliminated through breast milk has received such scant attention. As a result of this neglect, the practitioner hears all sorts of speculative opinions about the effect upon the nursling of certain foods ingested by the mother. Fresh fruits and vegetables in season, as well as a long list of drugs have been incriminated as causes of colic.

The transmission of drugs through breast milk is of special importance to the clinician, since he is often called upon to medicate the mother without transferring this medication to the infant. If on the other hand, the breast milk can be used to introduce remedies of therapeutic value to the nursling then by proper regulation such a procedure may prove an excellent method of therapy.

Holt[1] says: "Elimination of drugs through milk is somewhat uncertain and variable. Few of those popularly supposed to affect the child through milk really do so."

Koplik,[2] Grulee,[3] Griffith,[4] and others also confirm the opinion that very little is known in regard to the appearance of drugs in breast milk, and that a great many of the statements in this respect are largely contradictory.

On the other hand Dunn,[5] Morse,[6] and Kwit and Hatcher[7] present evidence that when drugs are transmitted through breast milk, there are only traces present which do not have any effect on the infant.

The following problems present themselves for clinical investigation:

1. Is it necessary to remove the child from the breast because of drugs

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administered to the mother? In other words, if drugs are transmitted through breast milk, can their effect become injurious to the child?

2. If it is possible for certain drugs to pass through breast milk, would it be desirable to attempt to medicate the child by means of drugs administered to the mother? The latter would be an advantage, for it is well known that the giving of medicine to infants is at times attended with many difficulties.

Anticipatory to the clinical and chemical investigation, a questionnaire was mailed to 500 pediatricians and obstetricians in the United States. This was done to obtain some idea as to the relative experience of clinicians in this field of investigation. Of this number 351 answers were returned, and a summary was obtained as follows:

QUESTION 1. From your experience, do you know of any specific instances in which cathartics administered to lactating mothers were transmitted through their breast milk and produced a laxative effect or colic in the nurslings? If so, will you kindly give details?

ANSWERS:

115—Yes		192—No	
41—were questionable		3—did not answer	
Licorice powder	3 instances	Milk of magnesia	10 instances
Castor oil	12 instances	Aloes	5 instances
Phenolphthalein	16 instances	Lady Webster pills	1 instance
Saline cathartics	17 instances	A.B.S. & C. pills	1 instance
Cascara	40 instances	Rhubarb	2 instances
Vegetable cathartics	3 instances	Sal Hepatica	1 instance
Aloin	4 instances	Calomel	2 instances
Podophyllin	1 instance	Alophen pills	4 instances
Jalap	1 instance	Ex-Lax	1 instance
Citrate of magnesia	7 instances		

QUESTION 2. Do you know of any specific instances (not speculative) in which fresh fruit in season, or canned fruit, or foods taken by a lactating mother, produced a laxative effect or colic in her nursling?

ANSWERS:

50—Yes	269—No
19—were questionable	13—did not answer

QUESTION 3. Do you know of any specific instances in which any drug other than cathartics or laxatives administered to lactating mothers was transmitted through their breast milk, and produced an untoward effect in the nurslings?

ANSWERS:

76—Yes	240—No
18—were questionable	17—did not answer

The first part of our study was devoted to laxatives, which is the subject of the present report. This includes the following: aloin, phenolphthalein, calomel, cascara, senna, and rhubarb.

The vegetable drugs (aloes, cascara, rhubarb, senna, and frangula) belonging to the anthracene derivatives, depend upon emodin (trioxyquinone of methyl anthracene) for their laxative and sometimes purgative effects.

The anthracene derivatives are of importance in habitual constipation, particularly of the atonic type, because even when the dose is not increased, repeated use does not lessen their effect to any appreciable extent. They are, however, of less value in cases of spastic constipation. After administration, they are partly absorbed and partly eliminated in the urine, to which they impart an alkaline reaction and reddish color.

Gottlieb and Meyer,[8] and Heinz[9] are of the opinion that a certain portion of the resorbed emodins are eliminated through the milk. However, the quantities eliminated are entirely too small to have a toxic or a purgative effect upon the infant.

Dreyfuss-See[10] remarks regarding the anthraquinones, that although no real effect, either toxic or laxative, is noted, it is better not to give them to nursing mothers.

Joachimovits[11] in his investigations on the presence of drugs in breast milk by means of fluorescent analysis under ultraviolet light, showed that aloes (one-half gram per dose) administered daily to a human subject could be constantly demonstrated in the milk, although rhubarb administered in therapeutic doses gave no positive results.

Dombrowsky[12] observed that after administration of rhubarb, the active substance may pass into the milk giving it a yellowish color. He concluded that chrysophanic acid passed into the milk. On the other hand Bucura,[13] who used the soda lye test for chrysophanic acid in milk, was unable to demonstrate its presence even after administering large doses of the extract or pulverized root of rhubarb.

Bucura also states that the active substances of cascara sagrada could not be demonstrated in the milk, neither could he detect phenolphthalein in the milk of two women who had received one-half gram daily for two days.

According to Cloetta,[14] cathartic acid passes into the milk after the administration of senna.

Kwit and Hatcher[7] gave phenolphthalein to five patients. Two received laxative doses of 30 mg., one received a dose of 60 mg., while the other two received doses of 90 mg. They say that no evidence of phenolphthalein in the milk was obtained even after the dose of 90 mg., although as little as 0.03 mg. per 100 c.c. of milk could have been detected with certainty.

EXPERIMENTAL

After a physical examination, patients in the maternity ward of Temple University Hospital were endorsed for this study, and only those patients having babies at the breast were utilized.

The first series of investigations was merely a clinical study. Immediately following delivery, the number of daily bowel movements for both

mother and child was recorded. These records were kept for each day until the patient was discharged.

On the evening of the fifth day cathartic was administered by mouth to the mother, in proper dosage to effect an evacuation of the bowels. Based on a comparative study of the character and frequency of bowel movements in the mother and child following the use of the laxative, deductions as to clinical effects were noted and recorded. In several instances it became necessary to discontinue the use of the laxative for the mother because of resultant diarrhea in the infant. Colic in the child and untoward symptoms in both child and mother received consideration.

A second series of investigations repeated all that was carried out in the first series, but with the additional factor of a chemical analysis of samples of breast milk after administering the laxative to the mother.

The drug having been administered on the evening of the fifth day after delivery, the first sample of breast milk was obtained at 2 A.M. on the sixth day and kept separate from all others. Beginning at the 6 A.M. feeding on the sixth day, and at the succeeding feeding hours of 10 A.M., 2 P.M., 6 P.M., and 10 P.M., a sample of breast milk amounting to one-half ounce for each feeding was collected, pooled, and retained as a composite sample for the day. This was then analyzed for the particular drug. This routine was followed each day until the mother and child were discharged.

According to Valaer and Mallory,[15] when one of the group of drugs consisting of rhubarb, cascara, frangula, senna, and aloes is made acid and extracted with ether, and the ether extract is made strongly alkaline with ammonia, a red color develops. Under certain carefully observed conditions the depth of color extracted by the ether and the color developed on the treatment with ammonia vary almost directly in proportion to the amount of aloes or emodin-bearing drugs present.

According to Hauser,[16] aloin and barbaloin are isomeric aloe-emodin-anthranol-d-arabinosides, $C_{20}H_{20}O_8$, in which the arabinose group $CH_2(CHOH)_3 \cdot CHO$ substitutes the H of the enolic OH in the two isomeric anthranols. Therefore, in testing for the aloin in the breast milk, Bial's test was used, the HCl of the reagent splitting off the arabinose group upon heating, and the resulting reaction for pentoses constituting the basis for a positive reaction.

Phenolphthalein was tested for by making the milk alkaline with sodium hydroxide. The addition of 0.02 gr. of phenolphthalein to 2 oz. of milk could be detected in this manner.

Mercury was tested for by the addition of alkali, by potassium iodide and by means of copper foil.

Cascara was tested for by the method before mentioned (Valaer and Mallory), which was sufficiently sensitive to detect the presence of 1

minim of fluid extract of cascara added to 2 oz. of milk. This corresponded to 1 gr. of cascara.

Senna likewise was tested for by this same method and positive results on control samples of milk were obtained after addition of 4 minims of fluid extract of senna to 3 oz. of milk. This corresponded to 4 gr. of senna.

Rhubarb also gave, with this test on control samples, positive results after the addition of 3 minims of syrupus rhei to 3 oz. of milk. This corresponded to 0.3 gr. of rhubarb.

Aloin.—In the administration of aloin the following prescription was used:

℞—Aloini U.S.P. gr. xxv
Sucrosi drachms ii
Misce et ft. chartulae C
Signa: One (1) powder before bedtime.
Each powder contained grain ¼ of aloin, which represents the average adult dose.

A series of 33 cases was originally run, on which no chemical control was attempted, and the results obtained as to effect on mother and child are shown in Table I.

TABLE I

EFFECT ON BOWELS OF	CONDITION OF MOTHER'S BOWELS BEFORE ADMISSION		
	REGULAR NO LAXATIVE USED	NOT REGULAR USED LAXATIVE	TOTAL
Both mother and child	7	2	9
Mother but not child	12	1	13
Child but not mother	2	0	2
Neither mother nor child	6	3	9

From this may be seen that from clinical observation alone the child was not affected in 22 cases or in 66.67 per cent of the total.

Another series of eleven cases was run on which chemical analysis of the breast milk was made during the period of aloin administration. The results are shown in Table II.

TABLE II

EFFECT ON BOWELS OF	CONDITION OF MOTHER'S BOWELS BEFORE ADMISSION			BREAST MILK CHEMICAL TESTS
	REGULAR NO LAXATIVE USED	NOT REGULAR USED LAXATIVE	TOTAL	
Both mother and child	0	1	1	1 positive
Mother but not child	3	1	4	1 negative 3 positive
Child but not mother	0	0	0	0
Neither mother nor child	4	2	6	2 negative 4 positive

From the clinical observation 10 cases of 90.9 per cent of the total showed no effect on the child, although 7 out of the 8 positive chemical tests fell within this group. The other positive finding being the one case in which both mother and child were affected.

Phenolphthalein.—A dosage of 1 gr. was used in these tests. The original series consisted of 25 cases, without any chemical tests being made, and the results are shown in Table III.

TABLE III

	EFFECT ON BOWELS
Both mother and child	5
Mother but not child	10
Child but not mother	5
Neither mother nor child	5

From these clinical observations alone the child was not affected in 15 cases or 60 per cent of the total.

A second series of 14 cases was run and chemical tests for phenolphthalein were made on samples of breast milk. The results are shown in Table IV.

TABLE IV

	EFFECT ON BOWELS	CHEMICAL TESTS
Both mother and child	5	Negative
Mother but not child	7	Negative
Child but not mother	1	Negative
Neither mother nor child	1	Negative

From clinical observations 8 cases out of the total of 14 (57.14 per cent) showed no effect on the child, and in all cases the chemical tests were negative.

Calomel.—Administrations of 2½ gr. were made daily. On an original series, without chemical control, a total of only 4 cases is available, with the results as shown in Table V.

TABLE V

EFFECT ON BOWELS OF	CONDITION OF MOTHER'S BOWELS BEFORE ADMISSION		
	REGULAR NO LAXATIVE USED	NOT REGULAR USED LAXATIVE	TOTAL
Both mother and child	0	2	2
Mother but not child	1	0	1
Child but not mother	0	0	0
Neither mother nor child	1	0	1

This series, of course, gives too few cases for accurate conclusions, but of the 4 cases, 2 (50 per cent) showed no apparent effect on the child.

The next series, during which chemical analysis of the breast milk for mercury was made, consisted of 10 cases. The results obtained are shown in Table VI.

TABLE VI

EFFECT ON BOWELS OF	CONDITION OF MOTHER'S BOWELS BEFORE ADMISSION			BREAST MILK CHEMICAL TESTS
	REGULAR NO LAXATIVE USED	NOT REGULAR USED LAXATIVE	TOTAL	
Both mother and child	3	1	4	Negative
Mother but not child	5	0	5	Negative
Child but not mother	1	0	1	Negative
Neither mother nor child	0	0	0	0

Here again 5 cases or 50 per cent of the total showed no effect on the child, and in all cases the chemical tests were negative.

Cascara Sagrada.—A dose of one fluid drachm was given daily. A preliminary series consisting of 12 cases was run, and no chemical analysis of breast milk made. The results obtained are as shown in Table VII.

TABLE VII

EFFECT ON BOWELS OF	CONDITION OF MOTHER'S BOWELS BEFORE ADMISSION		
	REGULAR NO LAXATIVE USED	NOT REGULAR USED LAXATIVE	TOTAL
Both mother and child	2	1	3
Mother but not child	3	3	6
Child but not mother	1	0	1
Neither mother nor child	2	0	2

From clinical observation alone we note that in 8 of the 12 cases (66.67 per cent) showed no effect on the child.

Then a series of 10 cases, controlled by chemical analysis of the breast milk, was carried out, and the results obtained are shown in Table VIII.

TABLE VIII

EFFECT ON BOWELS OF	CONDITION OF MOTHER'S BOWELS BEFORE ADMISSION			BREAST MILK CHEMICAL TESTS
	REGULAR NO LAXATIVE USED	NOT REGULAR USED LAXATIVE	TOTAL	
Both mother and child	3	1	4	3 positive 1 negative
Mother but not child	1	1	2	2 negative
Child but not mother	1	1	2	2 negative
Neither mother nor child	2	0	2	2 positive

Here but 4 out of the 10 cases (40 per cent) showed no effect on the child. Out of 5 positive chemical tests, 2 were on cases where neither mother nor child was affected; and the other 3 positive chemical tests were among the 4 in which both mother and child were affected. The other 2 cases where the child was not affected, and the 2 cases where the child but not the mother was affected showed no chemical reactions.

Senna.—Fluid extract of senna was given in dosage of 1 fluid drachm. A series of 10 cases was run and chemical tests were made on the breast milk. The results are shown in Table IX.

TABLE IX

EFFECT ON BOWELS OF	CONDITION OF MOTHER'S BOWELS BEFORE ADMISSION			BREAST MILK CHEMICAL TESTS
	REGULAR NO LAXATIVE USED	NOT REGULAR USED LAXATIVE	TOTAL	
Both mother and child	6	0	6	Negative
Mother but not child	3	1	4	Negative
Child but not mother	0	0	0	0
Neither mother nor child	0	0	0	0

Only 4 out of the 10 cases (40 per cent) showed no effect on the child by clinical observation, but the chemical tests were negative in every case.

Rhubarb.—The daily dose of Syrupus Rhei was 2½ fluid drachms. In this series, 9 cases were used and chemical tests made on the breast milk. The results are shown in Table X.

TABLE X

EFFECT ON BOWELS OF	CONDITION OF MOTHER'S BOWELS BEFORE ADMISSION		BREAST MILK CHEMICAL TESTS
	REGULAR NO LAXATIVE USED	TOTAL	
Both mother and child	0	0	0
Mother but not child	9	9	Negative
Child but not mother	0	0	0
Neither mother nor child	0	0	0

No effect was noted on any of the children in this series, and no evidence of a chemical nature was presented by the breast milk.

SUMMARY AND CONCLUSIONS

TABLE XI

	CHILD NOT AFFECTED		
	CLINICAL STUDY PER CENT	CLINICAL-CHEMICAL STUDY PER CENT	CHEMICAL TESTS POSITIVE PER CENT
Aloin	66.67	90.90	87.5
Phenolphthalein	60.00	57.14	0.0
Calomel	50.00	50.00	0.0
Cascara	66.67	40.00	40.0
Senna	----	40.00	0.0
Rhubarb	----	100.00	0.0

1. From chemical analyses no trace could be found of the transmission of phenolphthalein, calomel, senna, or rhubarb through breast milk.

2. Aloin gave positive evidence of transmission through breast milk, but 87.5 per cent of the positive cases gave no clinical evidence of affecting the child. Therefore the quantities transmitted were too small for any laxative action.

3. Cascara gave both chemical and clinical evidence of transmission, and it is therefore concluded that cascara can be transmitted through breast milk.

4. In the cases of aloin, phenolphthalein, and calomel, the clinical evidence in the chemical controlled series is in accordance with that found in the preliminary series.

5. Rhubarb gave no clinical evidence whatever, therefore it is concluded that no transmission takes place.

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FURTHER SUGGESTIONS FOR APPROACHING CHILDREN AND THEIR PARENTS: PART II

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THAT the psychologic and the physical parts of man are closely interrelated has for many years been almost an axiom in medical practice. Substantial proof of this* and a general acceptance of the principle have not, however, effected an appreciable application of this concept in our practical dealings with people. We tend to deal either with the bodily or with the mental aspects of any given case, but seldom do we deal effectively with both aspects at once. The result is that we often treat bodies on the one hand while ignoring (or perhaps actually damaging) the mind and the emotions, or we treat minds and emotions on the other hand while ignoring (or perhaps actually damaging) bodies. Good practice must proceed with full awareness of the interrelation between mind and body.

This is particularly true of good practice with children, since children are less able than adults to voluntarily control attitudes and emotions and are thus more subject to influence either from their own physical states or from psychologic impact made upon them by external situations or personalities. The physician has, therefore, in dealing with children an obligation to understand and deal with the psychologic aspects of his patient which is even more important than when dealing with adults. Perhaps some suggestions for gaining insight into the psychologic aspects of child life will be helpful.

One of the easiest mistakes to make in dealing with children is to throw them too readily into types for purposes of diagnosis and treatment. This is natural since we are taught in most of our courses in physiology and psychology that people belong to definite, clear-cut types like aesthenic or pyknic, stable or unstable, introvert or extrovert, and so on. In general this is, of course, true. But a too ready tendency to classify patients, particularly children, may cause the physician to make an inaccurate diagnosis or an inappropriate prescription.

Practically all children, for example, are extrovertive rather than introvertive, and extrovertive to a degree seldom encountered in adults. Whenever one finds an occasional truly introvertive child it is particularly necessary to deal with him wisely. Difficulty lies in the fact that many truly extrovertive children behave in an introvertive manner, or vice versa, because of the pressure of circumstance. Illness or lack of physical vitality may lead a child to behave as if he were lacking

*Dunbar, H. Flanders: Emotions and Bodily Change, 1935, Columbia University Press.

in mental and emotional vitality. Conversely, an unhappy child may behave as if he lacked physical vitality, whereas if happy he would be physically alive. We must not confuse these symptoms, jumping too quickly to conclusions about the type to which a given child belongs.

In the same way confusion may result about stability or instability. Quite stable children by congenital type may appear totally unstable if their physical or psychologic routine impinges too heavily upon their self-control. Conversely, unstable children can often be made to function on a stable basis if we control their environment and their attitudes sufficiently.

The danger in jumping to conclusions about types is that we are too likely to classify a child, and proceed as if nothing could be done to adjust his behavior. It is frequently true in dealing with adults that inheritance and lifelong circumstance have crystallized out a given type of functioning, and we are aided in diagnosis and treatment if we classify them within the boundaries of a given type, assuming that they will (and should) stay there. Children, however, are too malleable to make this a safe procedure with them. Quick classification gives the appearance of efficient, skillful diagnosis and prescription, but it often entirely misses the point. Unless we go deeply enough into each case to understand something of the forces, both present and past, that play and have played upon each child to make him what he is, we will too often miss the entire significance of his present condition, and will frequently prescribe something that will not fit him at all.

The same type of mistake can be made if one assumes too quickly that a given problem is functional rather than organic in nature, or vice versa. Let us illustrate this point with two examples, one in which a feeding problem, actually psychogenic in nature, appears on the surface to be physiogenic, and one in which the reverse proves to be true of a case of enuresis.

It would, for example, be natural to diagnose a feeding problem as physical in origin because the child belongs to a delicate looking family and is himself thin, highstrung, and undernourished. A few questions, however, may bring to light, for example, the fact that the parents consider good appetite an evidence of bestiality, that to be civilized one must live in the mind rather than in the body. This, rather than constitutional type, may be the reason for their physical appearance. To be "cultured," in other words, one must look "spiritual." Such an attitude would, naturally, lead to indifference toward selection and preparation of food, so that the child has before him not only an attitude of contempt for food, but actually badly chosen and unappetizing food. The problem here may look obviously physical, whereas it is actually psychologic.

On the other hand, a too quick conclusion that the bed-wetting of a child belonging to a highstrung, nervous appearing mother is psychologic may be, again, to miss the point. There are many mothers, particularly of the so-called middle classes, who cannot endure letting a child lie in a wet bed, even though the wetting may occur several times nightly. The physical fatigue of frequent night rising and of heavy laundry work every day may in time wear the average woman into a state of nerves which makes her look like a truly neurotic type. If a urine analysis for the child is negative, and a casual physical examination shows no obvious physical difficulty, we are likely to conclude that the neurotic mother is the cause of the trouble and to give her a sound scolding (thus adding to her state of nerves).

I have known many such cases in which the difficulty proved eventually to be some fairly obscure physical phenomenon. Although experts agree that from fifty to ninety per cent of enuresis cases are psychogenic, it is never wise to jump to the conclusion that any given case is because it appears so on casual examination. A few questions about the program of toilet training attempted, the results (or lack of results) obtained, the present schedule, the mother's temperament and personality before the child became troublesome, her present attitude toward the child and his problem, will usually help us to determine whether the mother's present nervousness is result, or cause of the child's problem.

It is extremely easy to lose patience with a so-called neurotic (by this we usually actually mean an apparently unreasonable, un-self-controlled) mother or child, and to allow either to feel our impatience. Frequently this is the one thing we should not do, since even if we have guessed right and the person is truly neurotic, an unsympathetic attitude only aggravates self-pity and increases nervous tension. If, however, we have jumped to a false conclusion, and the mother or child is not fundamentally neurotic, but only thrown temporarily off center by the force of circumstances, we may do the patient a serious injustice. More important than this, we may, through misunderstanding his true difficulty, fail to reach a satisfactory cure which with more patience and more insight we might have achieved.

For accurate diagnosis of behavior difficulties a history of the specific difficulty is helpful.

"When did the trouble begin?"

"Was there any peculiar attending circumstance?" (ex. gr., illness of child or someone else near him; change of personnel in the home; change of family fortunes or any other condition which would produce emotional and nervous tension in the home, and so on.)

"What has happened?" (i.e., when and under what circumstances was improvement or relapse noted; what has been done about the difficulty, and with what results?)

From such questions the doctor can often learn what the primary and secondary causes of the difficulty are, and enough of what the past and present circumstances are to guide him in suggesting further procedure.

It is important to know enough about the home setting to give one a picture of the circumstances, both physical and emotional, which surround the child. One method of treatment will work in one home but not in another depending upon the physical set-up of the home, the amount of attention the mother or other persons can and do give the child, the strains or harmony between the various personalities involved, and so on. Some treatments will work at one time and under one set of circumstances in a given home, but not at others; will work with some children, but fail with others; are helpful at some stages of the child's training, but useless, or even harmful, at others. In order to judge accurately what treatment to recommend to any given parent for any specific child, in any given family, at a given stage of development of the problem, one must know the relevant facts about that particular parent, that particular child, that family setting, and that problem. Ten or fifteen minutes of carefully chosen questions will give most of the essentially relevant information.*

Even though the doctor's schedule is crowded so that time becomes an important factor, and even though he seldom has facilities for gaining a firsthand knowledge of the child's home, play, and school life, a few simple questions can frequently throw significant light on fundamentally important aspects. Some of these questions will be asked anyway in connection with the physical aspects of the problem. One should learn to listen to the answers for their psychologic as well as for their physical implications.

"What time does the child retire? What time does he waken?" These two questions should tell something of the child's rest hours. The answers may indicate the wrong bed time, or the wrong place to go to sleep (some children are put to bed in a room too close to family activity which goes on after the child's bed hour), or any number of other illuminating facts.

Therefore, it is wise to add:

"Where does he sleep? In what kind of bed? With anyone? Does the bed mate wet the bed, talk in his sleep, etc.? When does the child get up?" (The answer to this question is often different from the waking time.) "How does he behave when he gets up? Pleasant and active? Or cross, slow, tired?"

*We appreciate that many psychologists and psychiatrists would insist upon many hours of questioning as a background for treatment. For cases which require highly specialized psychologic treatment this is true. We are assuming here that the general physician is dealing with such everyday problems as arise in the course of his practice, and will refer serious psychologic problems to the proper specialist.

"When does he eat breakfast? What does he eat? With whom?" (Many family tensions revolve about the breakfast table.)

"When does he leave for school? What time does school start? How far does he have to go?"

The last three sets of questions about waking and getting off to school may be the answer to his constipation problem, since time may not be allowed for a leisurely toilet period. An interesting percentage of children's constipation problems revolve not only around what they eat, but under what conditions, and around a tension in routine living, especially in the morning. Getting the child (and, perhaps, the family) up fifteen minutes earlier in the morning sometimes provides the cure.

"How long does the child have at noon for lunch? Does he come home for lunch or take it to school? If at school, what does he do with the rest of the noon hour when he is not eating?" For many overstrained children a modification of the noon hour routine will break the strain of the day at a most strategic point.

"What does he do after school?" The type of work or play indulged in at this time of the day often needs modification to provide either more out-of-door play and exercise, or more rest, as the doctor finds necessary.

Knowing the child's age, it pays to ask what grade he is in at school. Here is a rough (very rough) guess at his general intelligence. Children enter school as a rule at six years, progress normally one grade each year, graduating from the eighth grade at fourteen or fifteen (the latter age allowing for moving, absences from illness, etc.). If, for example, the child is eight in the fourth grade one may guess him to be superior (the average age for the fourth grade being nine years); or if he is ten, one may guess him to be slow—barring illness or reasonable absence, of course. However, only a good mental test can give us the real light we want from this age-grade information. What we really want to know is whether the child is under strain in school—whether he is trying to do work beyond his capacity, or under conditions which cause emotional strain. Many nine-year-olds in the fourth grade, for example, are at age-grade, but, being ten to fifteen per cent retarded mentally, are under great strain to keep up with their grade. We cannot know this from the age-grade estimation suggested above, but only from an adequate mental examination.

Not only should we know the child's ability and the load that is being put upon it; we should also know whether he has an antagonistic or inadequate teacher who is keeping him under strain; whether other children in the room or on the playground are taunting or bullying him; whether the children he is playing with are too strenuous for him.

Most mothers are capable of visiting school for a half day and giving us a report on specific points if we should suspect that the situation needs investigation.

It should be remembered in this connection that, to the child of school age, school is his job; and it is just as important to know what strains or satisfactions he finds there as it is to inquire into the vocational life routine of an adult who offers a prolonged or nonemergency health problem.

Another focus for questions should be the family relationships.

"How many people live in the household? In how many rooms?"

"Who, among these, has authority over the child?" In other words. "How many bosses does he have?"

"How does the child respond to each of these people?"

Here we look for evidences of strain, of antagonism or misunderstanding, of jealousy, and of other important emotions. We should look not only for unfortunate relationships but also for the best ones. One particular person (parent, sibling, other relative, or even the maid) may be best able to help the child.

Just as school is the child's job, so is his home his most persistent and influential environment, and the younger the child the more true this is, since he spends more time there and is more completely dependent upon the personalities there than is the older child. To all children, however, the relationship with their parents and, to a lesser but still important degree, with every person in the household, is of vital significance. Children, like the rest of us, require a feeling of belonging somewhere, of fulfilling some purpose in life. The beloved and protected child finds an ample sense of belonging in his home, and the fulfillment of purpose just in being a satisfaction to his parents. The unwanted child is starved and unfulfilled in a vital sense. On the other hand, the spoiled child may not find fulfillment, but rather frustration of these impulses in his home. The reason for this lies in the fact that children, again like all of us, have powerful counter emotional drives. As a counter emotional drive to their urge for security and belonging their impulse toward fulfillment may, and usually does, take an ego or power direction which cannot be satisfied just by belonging to someone who is proud of them. Hence children are driven to express something which is an inherent part of themselves and not a reflection of someone else's wishes. For the spoiled child the conquest at home has been too easy. He requires a larger scope or a harder battle in order to feel achievement, and his sense of security in complete belonging is not sufficient to overbalance his other urges.

It is important, therefore, to know what the situation of authority, self-expression, and affectional relationships is for any given child. What we need in childhood is enough domination by parents and other home authority to provide guidance and assurance, but not so much

that normal power urges or self-expressive impulses are frustrated. We need enough love to provide an adequate sense of secure belonging, but not so much that the child is cut off from other affectional contacts. For adequate personality development children need both love and discipline. Children must, for best growth, be loved deeply and in a manner clear to them. But they must also be disciplined.

There is much misunderstanding about the amount and kind of discipline children should have. Some people think children should obey their parents and other adults instantly and without question. These people usually feel that life is an exacting business for which children should be given a Spartanlike training in preparation. This may, perhaps, be true, but what the people of this school of thinking lose sight of is that life also requires judgment and independent thinking. The submissive child who obeys others without question may find himself in adulthood incapable of resisting a bad authority. These are the stool pigeons of criminal gangs or the submissive, withdrawn insane.

On the other hand, the aggressive child who obeys only because superior physical or psychologic force compels him to, may develop into the explosively resistant negativist or "aginer." These are the radicals who are against everything but extreme individualistic behavior; they are the aggressive, explosive insane; or are perhaps the people who cannot hold jobs because they cannot take any sort of order no matter how tactfully worded. Such are the products of the instant-unquestioning-obedience programs.

To avoid these evils, we have a school of thought in which people believe that no arbitrary authority should ever be exerted with children; that children should be left to learn from their own experience and should be encouraged to make up their own minds and to follow their own ideas about everything. These people forget that learning from experience is often a slow, wasteful process; that children because of their limited knowledge and thinking power often draw the wrong conclusion from a situation; and that self-expression is socially dangerous unless closely coupled with self-control and consideration for the rights of others.

The ideal authority situation should give the child the guidance of adult experience and wisdom wherever his own trial-and-error learning would be too costly in time, strength, or health; it should give the child practice in making up his own mind about situations which lie within the scope of his intelligence and judgment; it should, whenever reasonably possible, explain to a child the reasons for commands and requests, since only so can a child become more intelligent about the procedures of life. But it should also require occasional obedience, without delays or explanations, especially in emergencies.

One of the commonest faults of authority over children is in giving too frequent and too detailed orders. When this happens either one person nags, or too many people give commands to the child. Obedience to too many commands carries the same results in child character that obedience to too severe commands does. Too great submissiveness, or too great negativism, or nervous "jitters" results.

Methods of enforcing obedience vary from severe physical cruelty, to ineffectual and meaningless nagging, or to tactfully passing over disobedience. Authorities differ as to whether or not children should be spanked, some feeling that an occasional slap on hand or thigh or a light switching of the calves of the legs is specific, concrete, and effectual. Others insist that physical discipline of any sort, whether it be spanking or physical restriction, is disastrous to the child's morale and to his attitude toward his parents. All authorities agree that severe spankings have no place in the discipline of any child, and the more difficult the child the more reason there is for finding some form of discipline besides physical violence. Whenever possible the punishment or reward should be inherent in the deed, or in some form logically associated with it. Refusal to come in from play for a meal should logically, for example, result in missing the meal with no food until the next meal. However, carried to extremes, this "natural-result-of-the-offense" philosophy gets one into trouble, and more arbitrary means of discipline must sometimes be used.

Much more than this should be said about obedience, but this may perhaps point out to the physician the two extremes of view he is likely to encounter in parents, and give him one or two of the most convincing arguments with which to win resistant parents over to a saner relationship to their children. The main point to be achieved is an adequate guidance of the child without strain or unnecessary tension for either parent or child.

As has been said, love is as important as discipline. The parents' attitude of affection toward the child often holds the explanation for trouble or for smooth happiness. Some parents are selfish as individuals, or are so much in love with each other that they concentrate on their own interests and neglect the child. This affectional neglect is often subtle, and occurs in some homes where parents conscientiously feed and clothe their children. In such homes the children may be given every surface evidence of loving care, yet may in reality be exceedingly lonely, and may even feel in the way. In another type of home the parents may love their child deeply, but, hesitating to spoil him, may maintain such an off-hand manner with him that he does not feel their love. This is likely to happen when the parents are of New England or other types of reserved backgrounds, or when the parents are for some other reason inhibited in their ability to express affection. When the

child lacks security in the knowledge that he is loved and wanted he is likely to react in one of two extreme ways. Either he withdraws into himself, trying to convince himself that love is not important and that he can get along quite well without it, or he takes up a restless search for affection in any direction which lies open to him.

On the other hand, many parents love their children oppressively and in the wrong way. Some of these see themselves living again in their children, and by absorbing the child attempt to capture vicariously whatever was missed in their own lives. A child thus absorbed is never free of parental dominance and solicitude. Other parents in this too-much-of-the-wrong-kind-of-love category smother their children with physical caresses, thus often gaining an erotic satisfaction not obtained in the spousal relationship. Such parents usually try to possess such children psychologically, cutting them off from personal contacts which might offer competition. Oddly enough, children of over-affectionate parents, like children of under-affectionate parents, react in either of two extreme ways. They will either yield to the hothouse atmosphere by becoming excessively dependent upon a warm bath of expressed affection and appreciation, or they will come to feel affectionate advances as unnecessary and undesirable interferences with one's freedom. In either case the child is poorly prepared for marriage.

More important to the immediate problem with which the physician is likely to be concerned, however, is the fact that the child whose affectional life is wrong almost invariably shows evidences of emotional disturbance which affect him both physically and behavioristically. His reaction toward one extreme of behavior or the other will depend upon his physical and psychologic make-up. The aggressive, vigorous child reacts one way; the timid less vigorous child, in another. It is important, then, that the physician know something not only of the personal and emotional environment of the child but also of the child himself, in order to gain an accurate insight into the emotional aspects of the case.

One of the best ways to gain insight into the peculiar make-up of the child is to inquire into his interests and activities.

"How does he spend his time when he is not occupied with the routines of sleeping, dressing, school, etc.?" The answer to this question will often tell us whether we have a naturally active or passive child, a natural physical or intellectual bias, a sociable or a solitary child, a free or a parental-dominated child, and so on. It may also reveal not only important psychologic insight, but reasons for fatigue on the one hand or for listless inaction on the other. Many children get well when we can give them adequate outlets and satisfactions in less fatiguing ways than they have been finding. Other children recover when we learn enough about them to rouse activity and interest to replace inaction and boredom. What has been said above about the necessity of maintaining adequate ego satisfactions should be remembered here.

This understanding of natural interests and talents becomes particularly necessary in dealing with children whose physical powers are limited and who are, therefore, cut off from the opportunities for vigorous physical expressiveness which serve to satisfy or fulfill many children. Each child should have some medium, or preferably several media, through which he can find satisfaction in accomplishment. To reduce fatigue by ordering a child off the playground and away from physical activity will, unless we substitute other satisfying activities, often only aggravate restlessness and nervous fatigue. Sedatives can be called upon to reduce rest*less*sness, but often we can achieve rest*ful*ness without them if we are skillful enough in dealing with each child to provide him with quiet, yet thoroughly satisfying "busyness."

This simplicity of approach is particularly necessary in dealing with children, who are even more dependent than are adults upon the happenings of their daily lives for the tone and regulation of their health. Too much cannot be said in dealing with children about the necessity for simple, straightforward procedure. It is interesting to note that the greater the maturity and knowledge of the physician the more simple his attack on the problems of his patients. It is necessary, of course, to have the great technical training of medicine in order to deal with specific illnesses and problems of a technical-medical nature whenever they occur. No physician can afford to allow his technical knowledge to lapse. But the truly great physician is quite as ready to deal with the simple, everyday problems of routine, and of daily living in his patient, since he knows that here he often finds the key to health or illness, and to happiness or misery. Wise physicians are doctors of happiness as well as doctors of health, since the two cannot be separated in most human lives

Critical Review

TUBERCULOSIS IN CHILDREN

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IN APPROACHING the preparation of a review of the year's literature on tuberculosis in children, a quotation by Corper,[1] credited to Gregory, seems particularly applicable. "The aim of science . . . is to find out and to expose so far as humanly possible why things are as they are and according to what rules events are shaped. . . . Even an imperfect and temporary explanation or hypothesis is much better than none at all, provided, however, that it be clearly recognized as a stage in the development of men's ideas as to the causes of things." The aims of science have had abundant opportunity for fulfillment in the case of tuberculosis. According to Long,[2] in his presidential address before the National Tuberculosis Association, man has been engaged in combating the disease in the clinic for two thousand years, in the laboratory for three hundred years, and in the field for fifty years. With what vigor the attack has been carried on along all three of these fronts in the last quarter of a century, is of common knowledge. To the student of tuberculosis the evolution of the ideas and experiences of the many workers in these various fields is indeed a fascinating one. How soon the combined efforts of all of them will succeed in finding answers to the many complexities and problems yet remaining for solution, no one can say. Certainly a great deal of knowledge has been acquired, sufficient in the opinion of some writers to conquer the disease completely, if only the means were at hand to apply the knowledge already possessed. As Whitney,[3] statistician of the National Tuberculosis Association says, "I think we may look for a consistent decline in the next five years which should bring the tuberculosis rate to as low as forty per 100,000 in 1941 or 1942. Whether there is a level or residuum below which we cannot depress the rate further, is a moot point. Personally I cannot see why forty or thirty, or even twenty, should be quoted as the low point. Why cannot tuberculosis be eliminated as thoroughly as other communicable diseases if we persist in the known workable methods which have proved successful so far?" Beaven[4] says, "Tuberculosis among children is decreasing rapidly. If the rate decline continues, it will soon be a rare disease. This is apparently happening not because of any attenuation in the virulence of the organism causing tuberculosis, but because fewer persons are infected with the organism." He found the decline in the proportion of children with positive tuberculin reactions in two hospitals in Rochester, New York, during the years 1926 to and including 1934 to be 62 per cent. Similar results have been reported for other communities. Whether this or the next two or three generations sees the end of a struggle begun two thousand years ago, medical science may justly be proud of its record in the conquest of tuberculosis.

The literature of the year immediately past contains fewer new concepts about tuberculosis in children than it has in previous years.

Most of the material is concerned with the recording of experiences or of opinions relating to concepts already advanced. The success of the veterinarians in stamping out bovine tuberculosis is noted, and the application of this success to the human problem is discussed. Tuberculin receives an unusual amount of attention. The controversial subject of resistance in tuberculosis is approached from all angles, still with no unanimity of opinion. The British Isles furnish several excellent clinical and pathologic studies. A few authors submit studies containing valuable information relative to the fate of tuberculous infants and children. A possible new method of therapy with vitamin C has interested some workers, and will undoubtedly be of considerable interest to readers. The New York experiment with B.C.G. is brought up to date, and certain conclusions are drawn. While these items by no means exhaust the various phases of tuberculosis in children as encountered in the literature, they nevertheless are fairly indicative of the main interests, so that the purpose of this year's review may be considered to have been fulfilled if the important facts under each of these headings can be presented.

SUCCESS OF THE VETERINARIANS

The success of the veterinarians in eradicating tuberculosis from among cattle interests Myers,[5, 6] who sees in this work a hopeful parallel for the human problem. In 1891, only a year or so after the discovery of tuberculin by Koch, the work of testing cattle with tuberculin was begun in this country. On July 1, 1936, forty states were on the accredited list, which means that 0.5 per cent or less of infected cattle existed in any county in those states. By this year it is expected that all but two of the states, California and South Dakota, will have become accredited. It is apparent that the veterinarians in America have indeed accomplished a remarkable piece of work, when one recalls that among many herds of cattle 50 per cent or more were infected when the program was begun. The reasons advanced for this success are ascribed to the early adoption by the states of the plan which called for the slaughtering of all animals which reacted positively to the test, and for the repetition of the test at regular intervals in order that animals which might have been too recently contaminated to react to the first test, could be identified at the later one. It was necessary to overcome considerable opposition before this method gained general acceptance. Many felt that only sick animals need be slaughtered, but abundant proof was obtained at autopsy to show that healthy appearing but positively reacting animals harbored grossly or microscopically demonstrable foci of disease. Moreover, it was shown that when the Bang method of control was employed (the Bang method consists of slaughtering the ill animals, and segregating the positive reactors in a herd separate from the negative reactors), animals in the positive reacting group were constantly falling ill from the disease and becoming a source of contact for other animals. In England where the practice of slaughtering only ill animals has been in vogue, very little headway has been made. Myers[5] states that after two decades of this program it was found that approximately 40 per cent of England's cattle were still tuberculous. Thus a great deal of valuable information applicable to the human problem has been gained from the experiences of the veterinarians. The communicability of tuberculosis was early demonstrated; the specificity of the tuberculin test has

been proved beyond question; the importance of frequent retesting of negative reactors has been shown; and, a point of particular significance, latency has been demonstrated to be the period in which effective control measures lie.

TUBERCULIN

Many articles dealing with the subject of tuberculin have appeared in the year's literature, among the more important of which are reports of surveys; experiences with the new purified protein derivative (hereafter referred to as P.P.D.); and the meaning of the tuberculin test.

The Tuberculosis Committee of the American Association of School Physicians,[7] organized two years ago for the purpose of devising standard methods and stimulating interest in the tuberculosis problem among the school children of the nation, has begun its work by preparing a graphic map of the United States showing the incidence of positive tuberculin reactors among school children in the various states. The annual preparation of such a map is planned, and as the work progresses important information will be supplied as to the localities in which control procedures should be concentrated. A total of 1,124,363 reports of tuberculin tests have been received, and the number tested and the positive percentages for each state have been recorded. South Dakota has the lowest rate with 4.6 per cent positive out of 9,071 tests done. The highest rate was found in the states of Virginia, Maryland, and the District of Columbia where the percentages were 51.7, 42.6, and 46.4, respectively. The committee does not claim that their first survey is complete enough to reveal the actual situation as regards tuberculosis in all the states. If private physicians could be encouraged to report the positive tuberculin tests occurring among the children in their practices, the picture would be much more indicative of actual conditions. Eventually, the committee feels the majority of the citizens of the United States will be tested with tuberculin, and adequate physical and x-ray film examinations will be made of the positive reactors.

Another survey of national scope is one submitted by Whitney and McCaffrey[8] which is the final report of the tuberculin committee of the National Tuberculosis Association on the results of group testing with P.P.D. during the two-year period following June, 1934. This survey is significant, because it is the first time a testing program on a large scale has been carried out in which a standard tuberculin of uniform dosage, technic, and interpretation has been used, and furthermore the number of persons tested (56,688) is deemed sufficiently large to be of value in arriving at a reliable index of tuberculosis infection in the United States. The tests were made with both first and second strength P.P.D. Of 29,021 negative reactors to first strength tuberculin, 16.9 per cent became positive to the second test. In order to arrive at a reliable index of the infection rate for all ages, the authors adjusted the actual rates obtained from their groups according to the percentage distributions of age, color, and nativity classifications of the general population as shown in the census of the United States in 1930. The adjusted infection rate for the United States, based upon 56,688 persons tested in 30 states and the District of Columbia, is as follows: all ages, 47.0 per cent; under five years of age, 24.9 per cent; five to nine years, 21.6 per cent; ten to fourteen years, 28.4 per cent;

fifteen to nineteen years, 31.9 per cent; twenty years of age and over, 60.1 per cent. These are the figures to be quoted as representative of the general population of the United States.

Several studies on P.P.D. are worthy of mention, because they mark advances in attempts to establish the ideal tuberculin, and since tuberculin testing has come to be of such paramount importance in the whole tuberculosis problem, it is of course, highly desirable that the question of settling upon the best form of tuberculin be answered and be generally adopted at the earliest possible time. Long and Seibert,[9] the originators of P.P.D., on the basis of some 95,000 completed tests with this form of tuberculin, conclude that very few cases of clinical tuberculosis are missed by the test, and that the overwhelming majority of those persons diagnosed as tuberculous not only react to P.P.D., but react to the minute first dose which is 0.00002 of a milligram. However, they estimate that an additional 10 to 20 per cent of positive reactors will be discovered by retesting the negative reactors with second strength P.P.D. which is 250 times stronger, or 0.005 of a milligram. The second test is important in that it uncovers a few additional cases of progressive tuberculosis, and many contact cases who are infected but not clinically significant at the time, and in whom the degree of sensitivity is not marked. An interesting phenomenon surrounds the positive reactions to the second test, the significance of which, the authors state, is not clear. Apparently the reaction has an element of nonspecificity about it, since it can be obtained as well with a protein derivative of other acid-fast bacilli such as the timothy bacillus, a finding which is not so when the protein derivatives are in the strengths of the first dose, 0.00002 of a milligram. Furthermore, the increment of reactions gained by the second dose is approximately constant in terms of the total number of subjects tested, regardless of the number reacting to the first dose. It is possible that such nonspecificity may result in a certain number of false positive reactions being included among the true positive reactions.

These authors have also experimented with various intermediate strengths of P.P.D. in an attempt to find a single dose which would satisfactorily detect those infected with tuberculosis without giving rise to undesirable severe reactions. They conclude that "the safe dose varies for different parts of the country, where different degrees of tuberculization of the population prevail, and for different social groups in the same locality." In communities where less than 40 per cent react to the two doses, a dose one-tenth as large as the standard second dose, that is an intermediate dose of 0.0005 of a milligram, appears practical for case-finding purposes and surveys for significant contacts; but in the eastern states where the incidence of tuberculosis and the corresponding number of close contacts is relatively high, a dose ten times the official first test dose, or 0.0002 of a milligram may be sufficiently potent to be practical and may be relied upon to detect about 90 per cent of the total reactors without risk of an undue number of severe reactions. Plunkett and Siegal[10] of the New York State Department of Health report their experiences in search of a one-test dose of P.P.D. for use in their statewide chest clinics. A previous study conducted by Deegan,[11] also of the New York State Department of Health, had shown that 0.001 of a milligram of P.P.D. had produced 185 or 12.5 per cent four plus reactions out of a total of 1,480 positive reactions obtained in testing 3,029 individuals to this single dose. It

was concluded that this was too high a proportion of severe reactions, and that further study was indicated. In view of this work the authors then began an investigation to compare P.P.D. in doses of 0.00002, 0.0005, and 0.005 of a milligram with old tuberculin in doses of 0.004, 0.1, and one milligram. In testing 1,747 persons it was found that the first dose of P.P.D. found two and one-half times more reactors than did the first dose of old tuberculin, but that little difference occurred in the number of reactors secured with the second and third series of tests. From a practical viewpoint it would seem that this study might have been more significant if the first dose of old tuberculin had been 0.01 of a milligram, since this is the usual first dose of old tuberculin recommended for clinical use. The total number of reactors found in the study was 1,069, of which 72.7 per cent were discovered by the first dose of P.P.D., and 93 per cent by the first and intermediate doses together. There were 15 four plus reactions with the first dose of P.P.D. and 13 with the intermediate dose of 0.0005 of a milligram. Many three plus reactors in the first series of tests were not retested because of the risk of incurring the undesirable four plus type of reaction. The authors conclude that "still further study is indicated in order to determine the size of a practical one-test dose of P.P.D. which will produce the maximum number of reactors with a minimum of severe reactions. From this investigation it appears that such a one-test dose may be less than the second dose of P.P.D., or 0.0005 of a milligram, which we used."

Further evidence that P.P.D. is equal if not superior to old tuberculin is presented by Law and Cory[12] and by Steele and Willis.[13] The former compared results obtained by the intracutaneous use of P.P.D. in its two strengths with old tuberculin in the commonly used dosages of 0.01, 0.1, and one milligram. In 300 tests the first strength P.P.D. gave results corresponding more closely to 0.1 of a milligram of old tuberculin than to 0.01 of a milligram in its ability to find reactors. In 275 tests the second strength of P.P.D. found more reactors than did one milligram of old tuberculin. The authors conclude, therefore, that P.P.D. is well adapted to accurate quantitative tests. Steele and Willis compared P.P.D. and old tuberculin by the Pirquet method. Corresponding results were secured when P.P.D. was used in a strength of ten milligrams per cubic centimeter, and old tuberculin was used in its undiluted form.

Harrington, Myers and Levine,[14] and others,[15, 16] have given excellent summaries of the present-day meaning of the tuberculin test. At the risk of repeating a familiar story to many, there may be some justification for presenting the significant points in these articles because of the importance which this test has come to assume in the control of tuberculosis, and because of the prominence assigned to it in the year's literature. The test becomes positive from the third to the seventh week after infection with living tubercle bacilli takes place, and it remains positive with few exceptions throughout the life of the individual, due to persistent viability of bacilli within the primary focus or in the associated lymph nodes. According to Harrington and his associates, nothing ordinarily taken into the human body causes sensitization of the tissues to tuberculoprotein except tubercle bacilli themselves which are resulting in or have resulted in tubercle formation. Dead tubercle bacilli or the protein content of tubercle bacilli may produce sensitization artificially for a short time, but the tissues

remain sensitive only as the result of the continuous production of tuberculoprotein from living tubercle bacilli. Under certain conditions sensitivity may become depressed, necessitating larger doses of tuberculin to elicit a positive test, or the tissues may become desensitized altogether. It is possible, although probably of infrequent occurrence, that a primary complex may heal completely, which would mean that all the tubercle bacilli had been killed. In overwhelming tuberculous infection such as is seen in pneumonia, meningitis and miliary disease, sensitization is usually depressed. In chronic forms of the disease in terminal stages, overproduction of tuberculoprotein may desensitize the tissues, and again in certain of the exanthemata, such as measles and scarlet fever, sensitivity may be temporarily depressed.

Some difference of opinion seems to exist as to the significance of variations in the intensity of the reaction. Stewart[17] does not believe that large and intense intracutaneous reactions are necessarily indicative of greater or more active tuberculous lesions. Opie and McPhedran[18] on the contrary conclude that "the probability of grave tuberculous infection increases with the severity of the tuberculin reaction." Both of these opinions were given after studies conducted on children. Schick[19] says, "In active tuberculosis the sensitiveness to tuberculosis is usually very high; 0.1 c.c. of 1:10,000 gives already a relatively intensive reaction. In less active cases and arrested cases the sensitiveness to tuberculin may be lessened and 0.1 c.c. of 1:2,000 is necessary to get a positive reaction. Two or three years after complete arrest of the disease, sensitiveness may be much lower and one milligram of old tuberculin has to be injected." More recently Wells and Smith[20] conducted an investigation among 4,906 children in Kingston, Jamaica, and found "a definite and significant upward trend in the per cent of tuberculous infection, both latent and manifest, with increasing severity in the tuberculin reaction." This point obviously needs further elucidation.

A positive tuberculin test is proof only that a primary complex exists somewhere in the body. The extent of the tuberculous process must be obtained by other means. Harrington and his associates state that they "no longer recommend making x-ray films of the chests of children except for the detection of developing reinfection or the clinical type of tuberculous lesions. Since this type of lesion is found in the chests of children who are positive tuberculin reactors only once in 2,000 or 3,000 examinations, it is hardly worthwhile to make x-ray films of the chests of children, since there are other age periods in life when films reveal so much more evidence of clinical tuberculosis. For example, during the high school age period one may expect to find evidence of developing clinical disease in one in every 500 to 800 positive reactors. In the college age period a larger number of positive reactors is found to have developing or well-established clinical disease, whereas in the twenties and thirties one may find a case of clinical tuberculosis in every 100 or 200 positive reactors." According to these writers the tuberculin test is of the utmost importance in the epidemiologic control of tuberculosis in the human family as it is in the bovine family. Tuberculin surveys of a community give a far greater accurate index of the degree of tuberculization in the community than do mortality or morbidity statistics. The knowledge that children have positive tuberculin tests may be used in two ways in the tuberculosis control program. Of first importance is the fact that leads are given as

to the sources responsible for the child's infection. The younger the child the more likely it is that the contaminator will be a member of the immediate family. In older children the chance of extrafamilial contact increases. For this reason tuberculin surveys conducted on children in the entering classes at school may be somewhat more productive in case-finding campaigns than are surveys in later grades. The second use of the tuberculin test is that close observation of children who react positively to tuberculin as they reach young adult life may permit the detection of clinical disease in a very early symptomless stage and before it has become communicable. In a group of children (averaging about eight years of age) who reacted positively to the tuberculin test, observed by the authors in 1921 and 1922, it has been found that approximately 10 per cent have already developed clinical tuberculosis. Still another field in which the tuberculin test has demonstrated its usefulness is in the study of contacts with known cases of tuberculosis. The familial nature of tuberculosis has been frequently alluded to in the literature by such writers as Opie and McPhedran. The important thing here, of course, is to x-ray the chests of infected contacts at least yearly from the age of puberty on to full adulthood in order that clinical disease may again be recognized at its very incipiency and treatment instituted before the communicable stage is reached.

PATHOGENESIS

In previous reviews the various ideas concerning the evolutionary course of pulmonary tuberculosis have been presented in detail, and hence need not be repeated here. All phthisiologists are agreed that there are two phases of tuberculosis; first or primary infections and reinfections; and they are likewise agreed that there are fundamental differences in the two types. However, not all are agreed upon the classification under these two conditions. Several authors in the past have suggested that the terms childhood and adult type tuberculosis, designated by the National Tuberculosis Association to indicate primary and reinfection forms of tuberculosis, are not as satisfactory as could be obtained. The Lymanhurst classification[21] has been presented in a previous review. Recently Miller[22] has given an excellent description of the classification which he uses on the tuberculosis service of Bellevue Hospital in New York City, and which he believes permits a better understanding of the pathogenesis and evolutionary course of pulmonary tuberculosis than does the classification used by the National Tuberculosis Association. The various types of tuberculosis are classified by him under the terms of primary complex, lymphohematogenous forms, transitional forms, and phthisical forms. His conception of the primary complex differs little from the usual understanding of this condition. Under lymphohematogenous forms he includes those types of pulmonary tuberculosis which result from the hematogenous spread of tubercle bacilli from the lymphatic pole of the primary complex. The route of such infection is usually from the tracheobronchial nodes upward through the large lymph channels and so into the vena cava at the venous angle. The pulmonary pathology produced is dependent upon the degree and frequency of spill into the blood stream. Acute miliary tuberculosis of the lungs is the result of a onetime eruption of tubercle bacilli into the blood stream in a massive dose. Protracted disseminated tuberculosis of the lungs results from repeated

blood stream dissemination, but in doses less massive than in the former type. Chronic disseminated hematogenous pulmonary tuberculosis is due to an occasional moderate discharge of bacilli into the blood stream. The pulmonary lesions produced by such hematogenous spread and the clinical course of the disease process serve to differentiate these forms from chronic pulmonary phthisis, although occasionally a phthisical lesion develops from a chronic hematogenous focus. Transitional forms of pulmonary tuberculosis are those in which such a gradual change occurs. Miller points out that any of these new or tertiary lesions are potential foci for further spread, similar to that seen in secondary lesions. Thus "it is obvious that the true conception of tuberculosis is not that of a static disease but rather of a potentially dynamic moving clinical picture, the nature of which depends upon numerous factors and conditions." Among these factors, dosage and tissue resistance are most important, with special emphasis being given to dosage.

Sharp differences of opinion continue to be expressed concerning the relative importance of such factors as natural resistance, acquired immunity, allergy, and dosage of organisms in the pathogenesis and evolutionary course of the various tuberculous processes. Myers and Stewart who have reported the majority of the results of many years of longitudinal observation for tuberculosis of thousands of children at Lymanhurst, are the leading exponents of the view that confines the classification of the first infection to the disease process resulting from the seeding of tubercle bacilli upon non-sensitized tissue. Reinfection forms of tuberculosis are the result of seeding of tubercle bacilli upon tissues previously rendered allergic by a primary infection. The source of bacilli in the reinfection types may be either exogenous or endogenous. They are impressed by the undesirable effects of allergy which in their concept is responsible for all the acute and chronic forms of destructive tuberculosis that produce illness and death. They are skeptical of the view that primary infections are beneficial in that they impart an acquired immunity to the host against chronic pulmonary tuberculosis or phthisis. In their opinion the human body is far better equipped to cope with tubercle bacilli in a state of natural resistance than it is as a result of any alleged acquired resistance imparted as the result of a previous primary infection. Some of the points in this concept of the Lymanhurst workers formed the basis for a panel discussion[23] before the annual meeting of the American Academy of Pediatrics at Kansas City in May, 1936. Dr. McCordock, a pathologist, and Dr. Dienes, an immunologist, expressed views somewhat at variance with the above concepts. Among the discussers opinions were voiced which are probably representative of the present day thinking. Such being the case it may be of some interest to present briefly the conflicting viewpoints.

Dr. McCordock stated it as his belief that "as far as the human species is concerned no useful natural immunity exists for either the human or bovine strains" of tubercle bacilli. The great majority of primary infections in children are brought under control by an acquired immunity which develops, usually, shortly after allergy. "In the early stages of the first infection, before the appearance of acquired immunity, the bacilli can grow without much restraint. There is then an interval between infection and development of acquired resistance during which the bacilli are able to grow unhampered by the defense

mechanism later mobilized by acquired immunity. This period of unrestrained growth is enjoyed not only by the bacilli remaining in the lungs, but also by those that have been carried to distant organs. A delay in the development of acquired immunity prolongs this initial period of active bacillary growth and may explain the presence of large caseous foci in some children who, to start with, have received only a relatively small infecting dose of bacilli." McCordock further maintained that the size of the infecting dose of organisms is of the greatest importance to the subsequent outcome of the disease in a child who undergoes a primary infection. Either the original exogenous dose may be massive, or it may become large from an original small dose as the result of the growth of bacilli in the body. An overwhelming dose produces progressive tuberculosis which ends fatally. Small infecting doses result in a healed primary complex and an active immunity. In between are those cases in which the bacilli are too numerous to be held in check by the degree of resistance developed. Such children run a protracted course which finally ends either with the progress of the disease being arrested, or with death occurring from some acute form of tuberculosis.

All the members of the panel were agreed that a primary infection should not be looked upon as a process which is localized to the lungs and regional lymph nodes. Hematogenous dissemination of bacilli to various distant organs in the preallergic and preimmunity period following the initial infection is the usual occurrence. Such foci pave the way for the later development of secondary forms of tuberculosis at a time when the initial lung and lymph node lesions have become quiescent or calcified. Dr. Dienes was of the opinion that the same mechanism comes into play in tuberculosis as in other infectious diseases which usually heal without causing permanent injury, in that the organism responds to the infection by developing specific immunity. The immunity response in tuberculosis differs from the immunity response in acute infectious diseases only in degree. In tuberculosis the organism is unable to rid itself of the infection and a small lesion probably remains throughout life, where it may flare up at any time.

Dr. Myers in defending his view of the forces which operate to bring primary infections under control states, "I am firmly convinced that it is the natural defense mechanism rather than any specific immunity which brings tuberculosis of the first infection type under control in such a high percentage of the individuals attacked by tubercle bacilli. The defense mechanism consists, first, of the neutrophiles, which ingest and focalize tubercle bacilli. As the neutrophiles die, they are surrounded and ingested by the monocytes, which soon become epithelioid cells. Next, there appears around the developing tubercle a wall of lymphocytes, the local connective tissue cells proliferate, and a fibrous wall is laid down; lime salts may be carried into the tubercle and finally invade the fibrous tissue capsule; even true bone may be deposited in this capsule. This, in brief, is the defense mechanism against tubercle bacilli. It has also been shown to be the defense mechanism against inanimate objects of the particulate type, such as particles of silica. Therefore, it is not a specific reaction against the tubercle bacillus, but the natural resistance which the body ever has present to defend itself against invasion from microorganisms and inanimate objects."

The next question discussed by the panel was the relation of acquired resistance to reinfection forms of tuberculosis. Dr. McCordock held the view that the immunity set up by a first infection is sufficient

to prevent the subsequent development of secondary forms of tuberculosis in the vast majority of instances. He says, "In most individuals primary infection produces a resistance which is well-nigh complete, and the disease is arrested. However, all immunity is relative, and a sufficiently large dose of virulent organisms will break down any immunity and produce active disease." Since at the present time one can hardly hope for a civilization from which all tubercle bacilli are banished, he believes it is better for the human race to continue to acquire immunity from primary infections, even though in so doing, some individuals must unfortunately succumb to the effect of the first infection. He fears that if primary infections could be prevented, a civilization might be developed which would be as susceptible to the ravages of a first infection as has been known to occur among certain aboriginal tribes brought into contact with tuberculosis, after having been raised in tubercle-free mountain villages. On the other hand Myers states, "In my opinion, the first infection type of tuberculosis can never be looked upon as a protection against subsequent attacks of reinfection type of disease. Indeed, it sets the stage for such attacks; first, by rendering the tissues allergic; and second, by harboring living and virulent tubercle bacilli for years, decades, or throughout the entire span of life. Just as long as the tubercle bacilli of first infection remain alive and virulent, they are definite liabilities to the body, and there is always the possibility that they may break prison at any moment and set up foci of the reinfection type of tuberculosis, resulting in illness or even death. Therefore, I am unable to see any benefit whatsoever from the first infection type of tuberculosis, and the sooner physicians and others stop arguing in its favor the earlier will tuberculosis in the human family be controlled."

Dienes pointed out that first infections, even of a size to be readily demonstrable clinically or roentgenographically, occurring in children previously uninfected, tended to heal without impairment of health, whereas reinfections of similar extent, occurring in adults who retain some degree of acquired immunity from a previous infection, usually resulted in a fatal issue. The explanation for such a paradox is not available at present. Many factors are probably responsible for lowering the specific immunity below the threshold sufficient to permit secondary lesions to develop. Among these are poverty, unfavorable hygienic conditions, pregnancy, lactation, and trauma. However, that secondary lesions do develop in a relatively immune organism is shown clearly by the fact that bacilli do not extend from such lesions to the lymph nodes, and if the lesions break down and bacteria are eliminated, they usually do not start new foci of infection. It is of interest to note Dienes' opinion on the much debated question as to whether tuberculin sensitivity and acquired immunity represent identical or separate phenomena. He says, "From a long study of tuberculin sensitiveness I came to the conclusion that allergy represents the development of active immunity in the tissues all over the organism." He is opposed to the view that allergy alone is responsible for necrosis of tissues exposed to the effects of tuberculoprotein. "In experimental work if the dose of bacteria is kept small, within the limits which might reasonably be involved in spontaneous disease, the most remarkable effect of tuberculin sensitiveness is a strong infiltration of

the tissues with mononuclear cells and the accelerated formation of tubercles. This type of response is characteristic of the active phase of immunity, and it is present just as regularly in animals sensitive to egg white as in tuberculous animals." Schick[19] expresses a similar interpretation of the significance of allergy. He defines allergy as meaning "altered reactivity." The organism reacts to the reintroduction of the tubercle bacillus quicker and better than at the time of the first invasion. The establishment of allergy represents a basis for improved resistance against superinfection from without or within.

Still another study bearing upon the problem of acquired resistance to tuberculosis is that of Reichle and Gallavan.[24] The objective of the authors was to test the validity of Ranke's concept of a blockade which, developing in the course of a primary infection tends to localize all subsequent lesions. The blockade was referred to as the lymphatic or hematic blockade. Autopsy findings on 81 persons dying of active tuberculosis in the Cleveland City Hospital from June, 1934 to July, 1935, provide the basis for the report. There were 8 cases of primary tuberculous infection, all of which showed massive necrosis of the lymph nodes, and six of which showed the presence of true miliary tuberculosis. Thus in these primary cases evidence of blockade, either lymphatic or hematic, was lacking. On the other hand, in 73 cases of reinfection tuberculosis, lymphatic blockade was established completely, or nearly so, in 45 cases, and hematic blockade in 49 cases. The efficiency of the blockade was found to vary with the type of tuberculosis present, being most efficient in the chronic forms, and less so in subacute pulmonary tuberculosis. The authors conclude that such results must be interpreted as a manifestation of resistance, even though the lung in cases of chronic pulmonary tuberculosis is often completely destroyed. The forces of resistance are sufficient to prevent spread beyond the organ attacked, but are not sufficient in all instances to prevent the development of clinical disease in organs whose preexisting channels of communication, such as the bronchi of the lungs and the tubes of the genitourinary tract, are avenues by which the disease is easily diffused. "Immunity in tuberculosis is therefore largely the result of a localization of the disease, certainly as much a sign of resistance as in the pyogenic infections, in which the development of an abscess demonstrates the ability of the body to localize the infection and the development of septicemia demonstrates an inability to do so."

In previous years numerous experimental studies upon animals have been undertaken in an effort to shed light upon this problem of resistance. Years ago Koch published his well-known report in which he showed that virulent tubercle bacilli, injected subcutaneously into guinea pigs previously infected with tuberculosis, resulted in a localized necrosis which healed more rapidly than did the site of the first injection of organisms. Known as Koch's phenomenon, this dictum was generally accepted until recently as positive proof that first infections do create a beneficial tissue resistance to subsequent reinfections of either exogenous or endogenous sources. Myers[6] questions the validity of such an interpretation of Koch's phenomenon with reference to tuberculosis in the human being. What may be ideal from the standpoint of a skin lesion in an animal, may require an entirely different interpretation when a similar lesion occurs in the lungs of a

human being. "Here the intense reaction frequently leads to necrosis; as in the skin, the necrotic tissue is often eliminated through a bronchus and a cavity remains in the lung. Everyone knows that this is likely to be a desperate situation, not only from the standpoint of prognosis but also from the standpoint of the patient's human associates, so much so that in therapy serious efforts are made to obliterate such cavities at the earliest possible moment." This past year Clawson[25] reports an animal experiment which he believes lends support to the theory that primary tuberculous infections as exemplified by Ghon tubercles are accompanied by the development of a marked degree of resistance. Rabbits were made allergic by injecting B.C.G. in one of four ways: subcutaneous, intravenous, intrapulmonary via the trachea, or intrapulmonary through the thoracic wall and pleura. Eight weeks later all allergic animals and a series of normal animals were given a subcutaneous injection of 0.01 of a milligram of a virulent strain of bovine tubercle bacilli. Forty-five days later the animals were autopsied. Tuberculosis was invariably present in the lungs of the normal animals in grades of from two plus to four plus, and in approximately half the animals the kidneys showed involvement to a similar extent. However, in the allergic animals the findings were entirely different; tuberculosis was present in only a few of the animals, and in grades of from one plus to two plus.

There is yet another phase of this problem of resistance to tuberculosis which merits discussion. This has to do with an interpretation of the observed fact that children between the ages of infancy and adolescence enjoy an unusual degree of freedom from phthisical forms of tuberculosis. Wallgren[26] advances the explanation that for phthisis to develop it is necessary that the age of puberty shall have been reached, thereby introducing the factor of endocrinology. Others express the view that it is merely the expected immunity effect conferred by first infections which may have become inactive or even obsolete. Myers,[6] however, has a different viewpoint, to the support of which he devotes an entire and extremely interesting article. He says, "The long period of time that is required for tuberculosis to develop into clinical disease in the human body probably is responsible more than anything else for the absence of symptoms and illness during the period of childhood up to adolescence." A similar course is observed in tuberculosis of cattle, swine, and fowl. Young cattle, pigs, and chickens, while they may be infected with tuberculosis as shown by the tuberculin test, do not fall ill with the disease until later in life. Veterinarians years ago learned that while calves and young cattle reacted positively to the tuberculin test, it was not until later in life that the animals became ill, and hence a source of contamination for other cattle. They also found that chicks who reacted positively to the tuberculin test did not develop tuberculosis in a communicable form until after eighteen months had passed. Marketing the poultry by this age has solved the problem of tuberculosis in this industry. Thus in animals as in man, it is not until adult life approaches that the destructive forms of tuberculosis characteristically make their appearance.

Except for the acute forms of reinfection type of tuberculosis, such as meningitis, miliary disease, and pneumonia, there is apparently a long period of time between the laying down of the primary complex

and the development of reinfection forms of tuberculosis of clinical significance. This appears to be true regardless of whether the primary infection occurs in childhood or in adult life. Indeed the interval may and frequently does extend throughout the whole span of life; but this interval must not be looked upon as one of complete inactivity of the disease, and therefore of no consequence. Rather it is a latent or smouldering stage with potentialities for producing clinical disease months or years after the original infection took place. Myers states that approximately 10 per cent of their children with positive tuberculin tests developed chronic pulmonary tuberculosis and were ill or dead by the time the majority was or should have been reached. If the morbidity continues at the same rate or is even somewhat retarded, at least 20 per cent will fall ill before they have lived out the span of life. He concludes his paper by saying, "Only recently we have come to consider seriously the potentialities of smouldering tuberculosis during the period of childhood. At one time we even looked upon the presence of this disease in the body of a child as an asset because we thought it to be a valuable immunizing agent. Now we know that once the primary complex has been allowed to develop, as manifested by a positive tuberculin reaction, there is no treatment of any avail; that is, the condition is beyond recall. Immunity does not develop sufficiently to destroy the tubercle bacilli. No treatment that we know, such as long periods of strict bed rest or even collapse therapy, destroys the tubercle bacilli in the lesions of the primary complex. Moreover, we have no practical method of permanently desensitizing the tissues of such persons. Our problem is no less significant than that of the veterinarian but where he solves it at once we must wait for further developments; that is, we must keep close watch for the development of the destructive type of disease so that if and when it occurs, treatment may be instituted before it becomes communicable or causes illness."

CLINICAL REPORTS

Opportunity to examine pathologically primary pulmonary lesions which are demonstrable roentgenographically, are not particularly frequent; hence, a case of Cameron's[27] in which he was able to do so is of especial interest. A seven-month-old infant died of a terminal tuberculous meningitis. An x-ray film of the chest taken four weeks previously showed a wedged-shaped shadow in the left upper lobe which was interpreted as "epituberculosis." At the postmortem examination of the lungs a typical primary complex was readily demonstrable. The Ghon tubercle was situated near the apex of the left lung entirely separated from the area of "epituberculosis," and already showed a concentric ring of calcium deposition. One of the associated caseous lymph nodes was firmly adherent to, and had broken into, the inferior surface of the wall of the bronchus supplying the left upper lobe. Extending outward from this point in triangular shape with its base at the pleura laterally, was an area of consolidation. No caseating areas were visible on its cut surface. Histologically the infiltration was composed of numerous endothelioid cells, a moderate number of fibroblasts and a few giant cell systems exhibiting minute caseous centers which had been invaded by fibroblasts and lymphocytes. Some evidences of retrogressive changes were visible. Only two acid-fast

bacilli were seen in a section of the stained lung. The author discusses the question as to whether this lesion was of the epituberculous variety (implying a potentially resolvable tuberculous pneumonia) or a tuberculous bronchopneumonia secondary to bronchogenic spread. Many authors in this country consider epituberculosis as synonymous with the collateral inflammatory reaction appearing about the primary pulmonary focus at or shortly after the development of allergy. Obviously Cameron's case was not of this type.

Dorothy Price[28] of Dublin, Ireland, draws attention to a significant point concerning mediastinal gland tuberculosis, derived from a study of 112 tuberculous children under five years of age. Some 200 x-ray films were taken of the group, of whom 36 died and 14 came to autopsy. Nineteen of the children died from miliary tuberculosis, 7 from tuberculous meningitis, 5 from a broken down primary lesion, and the remainder of causes not classified in the above. Of interest to Price was the fact that she found involvement of the paratracheal glands in nearly all of the fatal cases, whereas in those children whose radiograms showed only hilar gland shadows, much better results were observed. The paratracheal glands lie on either side of the trachea, and when sufficiently large show in the x-ray film at the level of the third and fourth ribs. They are the last in the drainage chain of glands of the upper mediastinum, those on the right emptying into the right lymphatic duct, and those on the left emptying directly into the thoracic duct. Preceding the paratracheal glands in the line of defense are the bronchopulmonary glands and the inferior and superior tracheobronchial groups, which collectively compose the hilar glands. The paratracheal glands thus stand between the hilar glands and the circulation in the defense mechanism. Roentgenographic demonstration of paratracheal gland involvement, therefore, should be regarded with grave suspicion as indicative of an imminent possibility of hematogenous dissemination of bacilli.

Contrary to the usual conception, Fish[29] calls attention to the fact that miliary tuberculosis need not necessarily lead to a fatal issue. More frequently than is generally recognized it runs a chronic course, and recovery occurs in a fair proportion of such chronic cases. Recovery may take place in generalized cases or even when the onset is moderately acute, although the outcome is more likely to be favorable when the disease is confined to the lungs. As proof of his assertions he cites 10 cases of chronic miliary tuberculosis in children, 6 of whom died, and 4 of whom recovered. In the fatal cases the duration of the disease ranged from five and one-half to eleven months. Microscopic sections of the lungs showed evidence of healed and healing miliary tubercles. Marked widening of the mediastinal shadow in roentgenograms was shown at autopsy to be due to numerous large paratracheal glands. Two of the children who recovered were three years of age, one was six, and the other ten. One of the three-year-old infants developed tuberculosis of the right elbow and of his cervical spine in the course of his miliary tuberculosis. Sixteen months after mottling was first detected in his x-ray picture he was in a fair general condition and had had a subnormal temperature for five months. The mottling cleared in the chest of the ten-year-old boy in eleven months, and in the other three-year-old infant after twenty-one months. The six-year-old boy had abdominal, cutaneous, osseous, and cerebral

tuberculous lesions in addition to his chronic miliary tuberculosis, yet he recovered at the end of three years. The author states that in the course of his hospital experience he has observed a considerable number of other similar cases which although not so convincing, nevertheless showed clinical and radiologic features strongly suggestive of the same condition in a milder form. He believes that with the spread of the practice of examining juvenile contacts by x-ray, cases of chronic miliary tuberculosis are likely to be detected with increasing frequency.

Blacklock[30] states that of 3,000 necropsies performed during the last twelve years at the Royal Hospital for Sick Children in Glasgow, 434 cases with tuberculous lesions have been investigated. It is interesting to note that only 6.4 per cent of a total of 2,055 necropsies done on children in the first year of life showed tuberculous lesions, but of those which showed such lesions 97.7 per cent died of tuberculosis. The incidence of tuberculous lesions was greatest in the three-year-old group, the rate declining somewhat for all subsequent ages. In 283 of the 434 cases studied, the route of the primary infection was the respiratory system, in nine the cervical glands, and in the remainder the intestinal tract. The primary pulmonary focus, wrongly called Ghon's focus, according to the author, since Parrot described it fully forty years before Ghon (Fried,[31] however, is of the opinion that the honor belongs to George Küss since he was the first to appreciate fully the significance of the primary complex) was present in 255 of the 283 respiratory cases. Only one focus was found in 231 of the cases, and for the entire 255 cases a total of 290 foci was found. In all the cases the hilar glands were involved and, as is the rule, the size of the glandular lesion was often in marked contrast to the small primary lesion. Only 10 per cent of the primary foci showed evidence to the naked eye of healing in infants up to one year of age, and none before six months. Thereafter, the incidence of healing increased rapidly. However, calcification was of relatively infrequent occurrence, being observed in only 26 foci, 22 of which were in children over three years of age.

The observation of two children with proved bronchiectasis who subsequently, at the age of adolescence, developed positive-sputa, prompts Dickey[32] to warn against the too ready exclusion of tuberculosis in children with sinus-lung disease.

Kretschmer[33] encountered 43 cases of tuberculosis of the kidney in children and adolescents. Fifteen of the cases occurred before the age of fifteen years, and 28 cases before the age of twenty-one years. There were 25 males and 18 females, although before the age of fourteen the number of males and females was practically the same. Evidence of tuberculosis elsewhere was obtained in 72 per cent of the series. Both kidneys were involved in 37.2 per cent of the 43 cases. The duration of symptoms before diagnosis was established varied from less than six months to as long as ten years. Frequency of urination was the most common symptom, being present in 37 cases. Nocturia was present in 32 cases; hematuria in 24; burning on urination in 19; pain on urination in 16; urgency in 10; fever, enuresis, and headaches in 5 cases each; and dribbling, incontinence, and difficulty of urination in 4 each. Urinalyses showed pus in 41 of the cases, albumin in 38, blood in 33, and casts in 8. The urine was sterile on culture in 19 or 44.1 per cent of the cases, but growths of various

types of organisms occurred in the remainder. Nephro-ureterectomy was carried out in 23 of the patients with no operative deaths.

PROGNOSIS, TREATMENT, AND PREVENTION

Information relative to the ultimate fate of infants and children infected with tuberculosis is always valuable, since such information gives the individual physician some degree of guidance in prognosticating his own cases. Three such studies are available for review. Those by Brailey[34] and Rosenberg and Kereszturi[35] deal with the mortality rate observed in the first five years of life, while Wolff and Hurwitz[36] conducted a follow-up study of 162 ambulatory children with tuberculous infection. Brailey's group of 170 tuberculin positive infants, of whom 72 were white and 98 were colored, was observed at the Harriet Lane House of the Johns Hopkins Hospital for the five-year period from 1928 to 1933. All of the children were found to be tuberculin positive before two years of age, the average age of the first positive tuberculin test being thirteen months. History of intrafamilial contact with an "open" case of tuberculosis was proved for about 78 per cent of the white and 64 per cent of the colored children. The difference in the mortality rate between the known exposed and those not known to have been exposed was insufficient to permit drawing any conclusions regarding severity of lesions in the more continuously exposed children. Thirteen per cent of the white children and 31 per cent of the colored children died in the five-year period; but approximately 70 per cent of the deaths fell within the first year of observation and most of them within the first six months following the discovery of infection. Children found to be infected before six months of age had a mortality rate of 33.3 per cent within the first year of observation, and of nearly 78 per cent within five years after the discovery of the infection. When infection was postponed until after six months of age or until the second year of life, the mortality rate was only 14 per cent within one year and 16 per cent within five years. Another factor influencing the mortality rate was the presence of a parenchymal lesion at the time of the initial x-ray examination. There were 67 such children in the series, of whom 31.3 per cent died within one year, and only one additional death from tuberculosis was recorded within the five-year period. There was little difference between the mortality rates of colored and white children showing parenchymal lesions, but nearly twice as many colored children developed parenchymal lesions. None of the white children died whose initial x-ray examination showed only bulging tracheobronchial nodes or was negative. However, 7 of the colored children whose x-ray findings were similar, died within the five-year period. All the deaths from tuberculosis were the result of the usual acute forms typical of this age period.

The report of Rosenberg and Kereszturi[35] presents the fate of 348 infants observed as part of the control group in the B.C.G. experiment which has been under way in New York City since 1926. The statistics for this group coincide very closely with those just given for Brailey's group. Seven per cent of the white children and 15.8 per cent of the colored children died during the first five years of life. No deaths from tuberculosis occurred in children over three years of age; 56 per cent of all the deaths occurred in the first year. Of the

infants infected during the first three months of life, 43.7 per cent died. Again, the mortality rate was highest in the group of patients whose roentgenograms showed parenchymal lesions. Of the white children with such lesions 25.9 per cent died, while the rate for the colored children was 46.7 per cent. More than five times as many children died when the x-ray films showed parenchymal lesions than when the films showed only enlarged tracheobronchial glands, and eight times as many as when the films showed no evidence of tuberculosis. From these studies then it may be concluded that a positive tuberculin test in an infant under six months of age is of serious prognostic import, and further that the presence of parenchymal lesions in infants, especially if accompanied by positive physical signs, calls for a similar serious prognosis. With these exceptions the prognosis for tuberculin positive infants is fairly optimistic.

If one contrasts the experiences with tuberculosis of the infants just cited with the 162 ambulatory tuberculous children followed by Wolff and Hurwitz[36] one realizes anew the extremely hazardous nature of tuberculosis in infancy, and its relative triviality in older children. Only one of the children in the latter group died, and that occurred in the youngest division; death was due to tuberculous meningitis. The ages of the 162 children varied from infancy to fifteen years; 88 were males and 74 were females. The average period of follow-up study was seven years. Over two-thirds of the children were known to have had intrafamilial exposure which was successfully interrupted in all but eight of the patients. At the initial x-ray examination 73 per cent of the films were classed as negative or doubtful, 15 per cent as latent, meaning that calcification or fibrosis was demonstrable, and 12 per cent as active. At the final check-up, one-half of the films were either negative or doubtful, 49 per cent showed latent lesions, and only 2 per cent remained active. Four of the patients who were initially positive to 0.1 of a milligram of old tuberculin became negative to tuberculin even in strong dilutions. At the conclusion of the study, with the exception of the one death, all the children were considered to be in perfect health but four, and of these only two had active pulmonary lesions. It is to be hoped that the authors will continue to keep this group of children under observation, because the ultimate fate of such infected children relative to chronic pulmonary tuberculosis is of the utmost significance.

For several years now the possible relationship of vitamin C to resistance in tuberculosis in both man and animals has been the subject of experimentation and speculation. Radford, DeSavitsch, and Sweany[37] state that the work was first undertaken to determine whether or not the peculiar resistance of rats to tuberculosis was in any way correlated with their ability to manufacture their own supply of vitamin C. Animal experiments seem to show clearly that an increased susceptibility to tuberculosis does occur when the diet is deficient in this element, and particularly so when scurvy is present. Studies on patients ill with tuberculosis[38] indicate that there is a decrease in the excretion of cevitamic acid, varying directly with the degree of severity of the disease. It is estimated that the normal elimination of cevitamic acid is approximately 20 mg. daily. Petter[39] tested a group of tuberculous individuals and found that only 3.6 to 8.74 milligrams were being eliminated. He then added 150 mg. of

chemically pure cevitamic acid to the diet each day which resulted, in an average of twenty-one days, in raising the urinary output of cevitamic acid to an average of 18.3 mg. When the additional vitamin C was withheld, the elimination of cevitamic acid in the urine decreased to less than 14 mg. The great majority of the patients who took part in the experiment, both adults and children, showed definite improvement while receiving the 150 milligrams of cevitamic acid. Radford and his associates, mentioned above, fed 500 c.c. of fresh orange juice to one group of tuberculous patients, 250 mg. of crystalline vitamin C to another group, and used a third set of individuals as a control group. Comparison between the groups was limited at the time of the report to the laboratory findings, with especial emphasis on the hematology. Judged by such criteria, the group receiving the additional vitamin C showed a greater degree of improvement. An editorial comment in the *Journal of the American Medical Association*[40] states that although the "evidence appears to indicate definitely the existence of an increased requirement of vitamin C in active tuberculosis, perhaps before final conclusions are drawn several other factors should be considered." Such factors include an investigation of possible increased excretion of vitamin C by routes other than the urine, such as sweat for example; and a consideration of the effect of the long period of fever in tuberculosis upon the vitamin requirement. Also it is desirable that the present method of estimating cevitamic acid be checked in order to prove its accuracy. It appears, therefore, that a rather significant finding has been uncovered which, if substantiated in further studies, may become of considerable importance in the therapy of tuberculosis as well as in the therapy of other diseases perhaps not as yet investigated.

There remains but one item to include in this year's review; that is B.C.G. The vast experiment which has been carried on for fourteen years in Europe, involving over one million infants and children inoculated with B.C.G. for the prevention of tuberculosis, is familiar to everyone interested in the subject. In this country the best known work with B.C.G. is that of Park and his associates who have conducted very carefully controlled and studied experiments for eight years in New York City. In spite of the favorable reports emanating from both of these sources, the prevailing opinion derived from numerous articles in the literature is that the use of B.C.G. should still be restricted to the experimental stage for the reasons that the harmful or protective influence of the allergy created by B.C.G. injections has by no means been settled; that certain animal experiments suggest that the B.C.G. organisms may regain virulency from residing in the bodies of their hosts; and that at least twenty-five years must elapse before any conclusive statement as to the efficacy and safety of the process will be justified.

Kereszturi and Park[41] after eight years' experience conclude that B.C.G. vaccine is harmless for the following reasons: large injections in 400 to 500 animals did not result in tuberculosis; 175 nonexposed young infants were vaccinated with B.C.G. and clinical tuberculosis developed in only one instance (and that was questionable); the observation period for this series of cases extended in some instances through eight years; in five children who died from tuberculosis out of 515 vaccinated but subsequently exposed, only human bacilli were

recovered from their organs; and finally, B.C.G. organisms recovered after living in cold abscesses in human beings for periods of from one to ten months, were still nonvirulent. In answer to the question as to whether B.C.G. is effective in preventing tuberculosis among vaccinated children, the authors point to their results. Among 269 orally vaccinated children there were three or 1.1 per cent tuberculous deaths; among 421 parenterally vaccinated children there were 3 or 0.7 per cent tuberculous deaths; whereas among 345 controls known since birth there were 9 or 2.6 per cent tuberculous deaths, and among 410 controls not known from birth with negative initial Mantoux tests there were 11 or 2.7 per cent tuberculous deaths. Thus the mortality rate of the orally vaccinated children was reduced to one-half that of the controls, and that of the parenterally vaccinated children to one-fourth that of the controls. Since the New York experiment has demonstrated the harmlessness of B.C.G. vaccine and a material increase in resistance to tuberculosis, the authors conclude "its use should be urged as a public health measure for the prevention of tuberculosis in those who have not yet become infected and who might later be exposed to tuberculosis in their own families."

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American Academy of Pediatrics

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Round Table Discussion of Meningococcic Meningitis

Chairman: Archibald L. Hoyne, M.D., Chicago, Ill.
Assistants: Edward B. Shaw, M.D., San Francisco, Calif.
Gilbert H. Levy, M.D., Memphis, Tenn.
Francis F. Schwentker, M.D., Baltimore, Md.

Meningococcic Meningitis

Archibald L. Hoyne, M.D.

Meningococcic meningitis is our topic for discussion. Possibly greater latitude in deliberations will be afforded if we assume that our subject is meningococcic infection. The latter term carries the inference that meningitis does not necessarily accompany or follow infection with the meningococcus. The presence of meningococcemia without clinical evidence of meningitis is not an extremely rare occurrence. The meninges as a rule are not the primary seat of infection, nor is blood stream involvement usually secondary to meningitis.

Interpretations which one places on this disease are likely to exert a marked influence in the choice of methods for treatment. Shall we apply therapeutic measures directly to the involved meninges, or should we attack the disease as a systemic one and indirectly relieve the meninges of their inflammatory products?

From the time that antimeningococcic serum was introduced some thirty years ago, it has been customary to administer the remedy by the intraspinal route in almost all instances. It seems that this was regarded as a necessity on the theory that the only value possessed by the specific serum was its antibacterial action. True, serum was sometimes injected by other routes, but generally intraspinal treatment was insisted upon as the standard procedure.

During a period of twenty-five years there has been considerable fluctuation in our mortality figures for meningococcic meningitis patients at the Cook County Hospital, in Chicago. With exception of one year in which there were but six cases, the fatality rate was seldom less than 40 per cent until the year 1933, when we began to make a change in our old established form of treatment.

Ferry in 1931 reported a soluble toxin of the meningococcus and developed a meningococcus antitoxin which he used experimentally in treating laboratory animals. In the fall of 1933 we began treating meningococcic meningitis patients with Ferry's antitoxin at the Cook County Hospital. Soon afterward we rapidly increased the intravenous dosage and at the same time diminished intraspinal therapy. Eventually all intraspinal treatment was abandoned. Now after a

period of about three years, during which no serum of any kind has been administered intraspinally, we feel more convinced than ever of the superiority of intravenous treatment exclusively.

We had success with intravenous treatment alone. Variations in fatality rates for the different age groups were noted. As in most diseases, the prognosis is particularly grave in the two extremes of life. This is especially true in meningococcic meningitis and is more apparent in those of advanced age than in the very young. Year, season, virulence of the organism, and degree of susceptibility of the individual are often given consideration in evaluating the success of any form of treatment. It is sometimes claimed the fatality rate is higher during an epidemic than when only sporadic or endemic cases are encountered. This has not always been our experience in Chicago.

When we consider such fatality figures as 95 per cent reported by the Ministry of Health of Great Britain for the year 1930 and the more recent report of Tripoli for New Orleans with a rate of 65 per cent, we feel that great improvement has been made during the past few years in the contagious disease hospitals of Chicago where intravenous therapy has been adopted exclusively.

Whether meningococcus antitoxin or standard antimeningococcus serum is used, the remedy is given in large doses—from 70,000 to 150,000 units of antitoxin or from 100 to 300 c.c. of serum—diluted in 10 per cent glucose in normal saline of at least twice the volume. To the mixture administered at body temperature, there is added about 10 minims of adrenalin. The rate of flow is often started at 10 drops per minute and gradually increased to 60 drops per minute. In this way we have sometimes given as much as 1,200 c.c. of serum to a patient within four days without unpleasant reactions. Some of our patients have received more than 2,000 c.c. of serum during their illness.

We feel there is no great emergency about making lumbar punctures if the clinical diagnosis is fairly certain. Blood cultures are made in every instance and, if they are negative, at least one lumbar puncture is done for the purpose of confirming the clinical diagnosis. We have treated fifteen or sixteen patients without resorting to any lumbar puncture, and in the group there was but one death—a fulminating case. Most patients have two or three lumbar punctures. Since discontinuing intraspinal therapy we have found no occasion to perform cisternal or intraventricular punctures.

Among the advantages noted with intravenous therapy exclusively are (1) almost a total absence of opisthotonos, (2) avoidance of difficult problems due to blockage, (3) fewer complications, (4) rarely any septic complications, (5) less discomfort for the patient, (6) more rapid recovery, and (7) lower death rate.

In respect to a choice between Ferry's antitoxin and a standard antimeningococcic serum, we no longer note the marked difference in the recovery rates originally observed. Possibly this may be due to some improved methods in producing the antimeningococcic serums. Nevertheless, among several hundred patients treated with the antitoxin thus far, we have not witnessed a single instance in which loss of hearing or loss of vision developed after antitoxin treatment was begun. This statement does not hold true for antimeningococcic serum treated patients.

A common objection to the mode of treatment described is its cost. There is no doubt that large quantities of antitoxin or antimeningococcus serum are expensive. But they are no more so than funerals.

However, we seem to be making real progress in the treatment of meningitis. We believe that intravenous therapy applied in the manner described reduces the death rate. Now chemotherapy, which has had advocates for many years, seems

to offer a means of reducing the cost of treatment without loss of efficiency. Fever therapy has also been resorted to, and a few satisfactory results have been reported.

There are others here to give you the benefit of their experience and to make more valuable presentations of this subject than I have been able to do.

The Theory of Treatment of Meningococcus Infection

E. B. Shaw, M.D.

The problem of treatment of meningococcus infection is directly concerned with peculiarities in their pathogenesis. Production of meningococcus disease proceeds through three phases, which may be sharply differentiated or may merge in several manners one with the other. Successively there is a period of onset, a second stage of dissemination (which may be transitory or indefinitely prolonged), and a final stage of localization (which is usually in the meninges). Certain observations indicate the manner in which the disease proceeds through these phases of infection.

Intense invasion of the blood stream by pyogenic organisms is commonly accomplished in a number of ways. Organisms are readily poured into the circulation from an infected lymph channel, vein wall, or heart valve, or they may be disseminated by means of infected emboli extruded from small thrombosed vessels which thus bridge the gap between local infection and the general circulation.

The nature of the primary focus of meningococcus infection suggests no such explanation for the extraordinary degree of blood stream infection which sometimes occurs. During the stage of sepsis meningococci may occur in the blood in tremendous numbers, are readily recovered by blood culture, and in contrast to almost any comparable condition are not infrequently demonstrable by careful direct examination of stained blood smears. The initial foci in the upper air passages are usually minute and obscure. There is little to suggest infection of vessel walls or thrombosis of vessels in a manner readily to explain the sepsis. Secondary disseminating foci are unusual.

Not only do the organisms easily gain access to the circulation, but they readily escape from it along with red cells and leucocytes in the production of the petechiae which characterize the sepsis. Examination of microscopic sections of petechiae fails to reveal the presence of thrombi or of bacterial or fibrinous emboli[1, 2, 3] but indicates that damage to the arteriole and capillary walls has resulted in a loss of vascular integrity,[4, 5, 6] permitting the escape of cells and organisms in the production of the eruption. In part this eruption is not frankly hemorrhagic but is due to localized loss of vascular tone; to this latter extent it may be blanched by an effective antiserum in a manner comparable to the effect of scarlet antitoxin on the rash of scarlet fever.

On several occasions I have seen other organisms enter the circulation or the meninges[7] along with the meningococcus, and, although these instances have not been very numerous, I believe that their occurrence is similarly due to vascular damage produced by the meningococcus.

The early pathologic changes in the meninges somewhat parallel the skin manifestations. Initially there are localized perivascular inflammation and minute areas of hemorrhage in the pia-arachnoid[8] as a preliminary to frank meningitis.

The conclusion is almost inescapable that in the initial focus of infection in a susceptible subject bacterial toxin is produced in sufficient amounts to effect vascular damage which permits ready entrance of the organism to the circulation and equally facilitates its escape to the perivascular tissues of the skin and meninges. After the infection has been well localized in the meninges, if the patient has survived the period of intense invasion, general symptoms of intoxica-

tion, including skin rashes, tend to disappear and the clinical evidence suggests that the toxin, initially very important, proceeds thereafter to play a somewhat less important rôle.

It would seem likely that an antiserum which was active against the specific toxin would be effective in arresting many of the manifestations of toxin activity, especially during the early stages of the infection. As a matter of fact the original antiserum used by Jochmann and Flexner, which was therapeutically very active, must have had a high degree of antitoxic activity. This antiserum was produced by the immunization of horses with suspensions of freshly grown cultures of virulent meningococci, no effort being made to exclude the soluble exotoxin from the suspension. Results of treatment with the antiserum so produced were apparently far superior to those secured with some later serums. A number of factors were blamed for this wane of therapeutic power, the cause commonly ascribed being failure of the serum to include properties specific against the clinical strain. At one time efforts were made to employ type-specific serum, but this proved not to be feasible because of the delay in treatment thus involved. Agglutination tests were formerly employed as a measure of the specificity of the serum against clinical strains, but it gradually became apparent that therapeutic properties did not parallel the strength of agglutination. Meanwhile methods of manufacture of serums had been altered so as to exclude toxin filtrates from immunizing suspensions. This practice eliminated unpleasant reactions and high mortality among immunized animals, and a serum was produced which was high in agglutinating activity but was therapeutically of relatively less value. A reversal of the trend in serum manufacture was accomplished by Ferry, who in 1931 distinguished the soluble toxin of the meningococcus and succeeded in producing an antitoxin. The application of this agent to therapy by Hoyne and others has led to excellent results with great diminution of mortality rates and the prevention of complications. I hope to learn in this round table a great deal more about these results and the indication for and technique of antitoxin administration.

Most of us have thought of the treatment of meningococcus infections in terms of bacteriolysis by serum. The theory of treatment with an antitoxin raises a great many questions which I should like to propose for discussion although I cannot pretend to answer many of them.

The actual onset of the disease is usually so obscure that no treatment can be proposed. In the stage of dissemination, sepsis, there is little question that a toxin is largely concerned with the breakdown of the host's resistance against invasion. In this stage antitoxin is extremely efficacious and the demonstrable value of any serum is largely dependent on its content of antitoxin. This stage of infection has always given the best evidence of the efficacy of serum—in answer to those observers who have sometimes held that antimeningococcic serum was lacking in therapeutic powers. Neutralization of toxin opposes the very property of the organism which is responsible for extension of the infection and for invasion of the meninges.

Early meningitis is a late stage of sepsis; at this time neutralization of toxin diminishes further flooding of the meninges. When the infection is well localized, organisms finally are eradicated from the blood stream, perhaps through increased resistance developed by the patient against the toxin. The presumption would be so great that at this final stage the antitoxin would be much less valuable although clinical results indicate that even at this time antitoxin is therapeutically active.

Clinically we recognize many infections in which the disease-producing activity of the causative organism is largely effected through the production of bacterial

toxins. The diphtheria bacillus produces a powerful toxin which is presumably nearly the entire cause of symptoms of diphtheria; early neutralization of this toxin completely arrests the progress of the disease. The streptococcus of scarlet fever produces a toxin which is responsible for many of the symptoms of scarlet fever but after neutralization of this single toxin there remain additional pathogenic activities of the streptococcus which may produce a variety of additional symptoms. A toxin is also produced in the course of erysipelas, but even more strikingly than in scarlet fever there may be progressive symptomatology after its neutralization. Certain strains of pneumococci produce specific soluble substances which may be neutralized with striking therapeutic effect, but thereafter pleural exudates may develop which are not strikingly affected by the use of antipneumococcus horse serum, which will not demonstrably enter or effect an empyema pocket. (In passing—it has recently been observed that rabbit antipneumococcus serum will enter and effect these cavities.)

Just where, among the various possibilities of antitoxin activity, does the action of meningococcus antitoxin belong? Clearly it is valuable in the early stages but is presumably less valuable at a later time. There are those who prefer to treat intravenously with antitoxin to combat sepsis and toxemia but who feel that in the meninges an antibacterial serum must be directly applied to affect this stage of localization. No completely satisfactory answer can be given to this question at present but there are several statements which are probably justified:

1. I have heard Dr. Ferry state that antitoxin serum is as strongly antibacterial as any of the serums in common use although the therapeutic usefulness of this property is difficult to evaluate.

2. Dr. Hoyne's results with intravenous treatment are just as satisfactory as any of the results with intraspinal therapy, and he thus avoids the production of intense meningeal reactions which are caused by intrathecal administration of serum. In the presence of meningococcus sepsis introduction of antiserum into the meninges before there is actual meningitis will not prevent invasion of the meninges but seems rather to accelerate it.[9] It is certainly not illogical to believe that an antiserum may reach infected portions of the meninges.

3. I suspect that the best answer at present is that neutralization of toxin is the only therapeutic result which can be effected with certainty and that once this is accomplished the patient's likelihood of recovery can be measured only by his own capacity to resist the further pathogenic activities of the meningococcus. It is not unlikely that somewhat after the manner of the streptococcus of scarlet fever, the meningococcus produces a toxin which injures the patient, is responsible for a fulminant onset, and prepares the way for later septic complications. Neutralization of this toxin materially benefits the patient, but there remains a residuum of additional pathogenic activities which may not be completely combated by antitoxin.

We must distinguish two varieties of meningococcus disease. In one, toxic signs predominate, petechial rashes are the rule, the patient may quickly succumb to the disease before there is meningeal invasion or early after it supervenes. Death is due in these cases to intoxication rather than to meningitis. These patients constitute a fulminant form of disease with high and early mortality, accounting for many of the forty-eight-hour deaths, but are especially—and often dramatically—susceptible to adequate treatment with antitoxin. Certain epidemics, perhaps certain localities, are especially characterized by this form of the disease, and it is the form most frequently encountered in epidemics.

In a second variety of the infection, generalized toxic symptoms are less notable; eruptions are less common; the diagnosis is usually made on the basis of signs of meningitis. These patients are not unaffected by serum therapy, but their response is less gratifying no matter by what route serum is applied. Such patients are especially encountered in interepidemic periods and although it is possible that their nature may be accounted for by delays in diagnosis I do not believe that this is the case.

It has been suggested that differences in strain of the causative organism are responsible for some of the differences in clinical behavior. The antitoxin is active against the toxins of all the various strains of meningococci, but some strains are better toxin producers than others. It has been stated that Types I and III are abundant producers of toxin, that in infection with these organisms characteristic toxic symptoms are the rule, and that they are more susceptible to antitoxin treatment. Types II and IV are said to be poorer producers of toxin, are more responsible for the sporadic form of the disease, and are less susceptible to antitoxin treatment.[10]

We need to know a great deal more about the relationship between strains and clinical behavior, the amount of toxin present in the given case and the rapidity with which it increases, and the quantitative relationships clinically present between toxin and antitoxin—the sort of information which is gradually being accumulated for the problem of pneumococcus therapy. How may the dosage of antitoxin be computed? Serum is expensive and large and repeated doses are not always well tolerated. How much is enough? Why should repeated doses be given? Diphtheria antitoxin is commonly given in a single dose. Should antitoxin be given only intravenously, or must we finally differentiate a form of the disease which must be dealt with as an empyema of the meninges?

I do not believe it is easy to answer all of these questions, but I think the clinician must finally supply the answers. I should very much like to hear the opinion of those with more experience in the use of antitoxin in the clinical management of these cases.

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Meningococcus Meningitis

Report of 176 Cases Treated With Ferry's Antitoxin

Gilbert H. Levy, M.D.

The increased incidence of meningococcus meningitis with its high fatality rates in the United States during the past ten years is worthy of due consideration. For the year 1934 United States Public Health reports listed 2,186 cases with 1,272 deaths, a mortality rate of 57.3 per cent. For 1935 the United States Public Health reports show 5,378 cases with 2,657 deaths, a mortality of 49.9 per cent, and for 1936 the number of cases were recorded at 7,203. The large cities of the country account for nearly 80 per cent of the annual deaths listed. Hoyne reports 4,028 cases for Chicago from 1916 to 1935, inclusive, with 47.7 per cent average yearly

fatality. Tripoli reports a mortality rate of 65.15 per cent for 221 cases treated at Charity Hospital, New Orleans, in the years 1925 to 1934. Gordon reported a fatality rate of 50.5 per cent for 1,686 cases at Detroit during the outbreak of 1928 to 1931. Mortality rates during 1929 for New York City, Salt Lake City, and Indianapolis were 48.6, 53, and 63 per cent, respectively.

At Memphis during the period of 1925 to 1933 the number of cases reported were 537 with 280 deaths. The fatality percentage varied from 35, the lowest, to 80, the highest. The average mortality was 52.1 per cent.

Clinicians identified with these various outbreaks prior to 1934 were disappointed with results obtained from standard polyvalent antibacterial serums. In the 1929 outbreak Anderson found ordinary commercial antimeningococcic serum therapeutically inadequate with a marked variation in the therapeutic value of the commercial serums. Hoyne has made similar observations at Cook County Hospital, Contagious Disease Department. We found in the 1930 outbreak at Memphis that intensive treatment with alternating injections of meningococcic serums, both intraspinal and intravenous, from five biologic firms, showed no specific differences in the serums. Intravenous injection of standard meningococcus serums was emphasized in the treatment of all cases seen early. The overwhelming toxemia and septicemic nature of our many patients justified its use. From such experience we believe, and have stated, that in all cases there is an early meningococcemia, admitting, however, the difficulty of proving this statement. Shaw and Thelander in a series of 58 consecutive cases of cerebrospinal fever in childhood over a ten-year period showed a high incidence of systemic invasion. These same authors suggest that vascular damage by manifestations of the infection permitted the characteristic blood stream infestations and the dissemination of the organisms. They conclude with the statement that "successful therapy should proceed from recognition of signs apart from those of meningitis and must be designed first to combat the intoxication and second to attack the organism more directly."

Ferry and his coworkers in 1933 studied the properties of bouillon filtrates of the meningococcus which resulted in the production of extracellular toxins specific to the four recognized Gordon types of the meningococcus as well as a toxin common to all types. When animals were injected individually with these four toxins, they developed antitoxins specific to the type injected as well as some antitoxin of the other types. They further demonstrated that meningococcus meningitis convalescent serums possessed neutralizing properties apparently specific toward homologous soluble toxins. Ferry showed that meningococcus antitoxin prepared by immunizing horses with meningococcus soluble toxin obtained from all four recognized Gordon types of the organism protected guinea pigs prophylactically and therapeutically against fatal doses of live cultures. A comparison was made with a lot of commercial tested antimeningococcic serum and controlled with normal horse serum. The experimental antitoxin afforded better prophylactic protection than the regular antimeningococcic serum. Antimeningococcic serum when injected in the same sized dose as the antitoxin failed to protect guinea pigs therapeutically against the fatal dose of culture, while the antitoxin protected the animal.

Further studies by Ferry and Schornack on guinea pigs, rabbits, and monkeys with meningococcus toxin and antitoxin indicated very conclusively that "the symptoms of meningococcus cerebrospinal meningitis in laboratory animals was due in large to the action in the central nervous system of a soluble specific toxin elaborated by the meningococcus and that these symptoms can be modified or entirely prevented by the neutralization of this toxin with a specific antitoxin."

Experimental meningococcus antitoxin prepared by Dr. N. S. Ferry was furnished us at the Isolation Hospital at Memphis in 1933. A preliminary report on twenty-four cases in 1933 and 1934 was read before the Georgia State Pediatric Society in December, 1935. Fourteen cases were treated in 1933 with two deaths and ten cases in 1934 with four deaths, resulting in a combined mortality of 25 per cent. The first eleven cases treated in 1933 resulted in only one death. Four of the six deaths reported occurred within twenty-four hours after admission. The ages represented ranged from eleven months for the youngest to forty-three years for the oldest. The average number of lumbar punctures required for treatment was 5.1 as compared to 6.9 in the 1930 series.

The average number of intravenous antitoxin injections was 1.1 as compared to 2.5 in the 1930 series. The average total spinal antitoxin injected was 86.7 c.c. (30,000 units) compared with 133 c.c. of standardized serum. All intravenous antitoxin was given well diluted in 10 per cent glucose solution. Sensitivity tests were made on all patients before administration of the antitoxin. The average injection was 10,000 units, or 30 c.c. Of particular interest in this small initial series was the short time, 4.8 days, required for the clearing of the spinal fluid from positive to negative cultures.

The apparent success of our first two years' experience with Ferry's antitoxin received an unexpected upset during January, 1935, when eight of the first nine patients admitted to Isolation Hospital died within a short period of time. Two of these patients were infants, one five months old and one eight months old. Seven of the eight were comatose on admission, extremely septic with advanced meningitis.

Our failure to combat the infection in the cases just mentioned was due to our lack of appreciation of sufficient intravenous dosage. It has been the custom since 1925 for all patients assigned to my service at the Isolation Hospital to receive antimeningococcic serum intravenously in small dosage, never averaging more than 30 c.c. This of course was in addition to the usual intraspinal serum treatments.

Hoyne in March, 1935, reported his observations on 296 cases of meningococcus meningitis, 85 of which were treated with experimental antitoxin (Ferry). The mortality for this entire series treated with antiserum and antitoxin was 39.5 per cent. Forty-three per cent of the deaths occurred within forty-eight hours after admission to the Cook County Hospital. The mortality of 85 cases treated with antitoxin was 23.5 per cent, whereas the mortality of cases treated with antiserum was 49.9 per cent. Twenty deaths occurred in 85 patients treated with antitoxin, and 97 deaths occurred in the serum-treated group comprising 211 patients. Hoyne advocated the intravenous use of 60 to 100 c.c. of antitoxin in 120 to 200 c.c. or more, respectively, of physiologic solution of sodium chloride or 10 per cent dextrose solution. The smaller dose for a child, the larger dose for an adult. This form of treatment may be repeated daily if the condition of the patient requires it.

Encouraged by the above results, we rapidly increased our average intravenous antitoxin to 81.3 c.c. or 28,000 units as compared with 30 c.c. or 10,000 units dosage used in 1933 and 1934. The intraspinal therapy average was 95 c.c., or 30,160 units, about the same quantity used in 1933 and 1934. Sixty of these patients with 29 deaths gave a fatality of 46 per cent. Excluding the 13 deaths in less than twenty-four hours and 4 deaths in less than forty-eight hours, the fatality was 26 per cent.

The smallest intravenous dosage in any single case in 1935 was 10 c.c. or 3,300 units. The largest intravenous dosage for one case was 525 c.c. or 175,000 units. Two cases in this group were recurrent, and both patients died. One of these patients, a white female, aged nineteen years, on her second admission received a total of 525 c.c. or 175,000 units intravenously and 285 c.c. intraspinally. This patient developed a bacterial endocarditis, suppurative pericarditis, optic neuritis, and complete deafness before death. At autopsy 200 c.c. of pericardial pus was obtained.

Of interest was a seventy-four-year-old white male, a transient, admitted in coma, who was given 100 c.c. of the experimental antitoxin intravenously and 150 c.c. intraspinally. This patient developed a right panopthalmitis which necessitated an enucleation. The patient made an uneventful recovery.

During 1936 seventy patients were treated with twenty-three deaths, giving a fatality of 32.8 per cent. Included in this group were seven patients who died within twenty-four hours and 4 within forty-eight hours after admission. Excluding these eleven cases, a mortality of 20.3 per cent would have been obtained.

At this time our average intravenous antitoxin therapy was increased to 159 c.c., or 53,000 units. This is five and one-half times the dosage employed in 1933 and 1934. The intraspinal antitoxin average dose was decreased to 60 c.c., or 20,000 units. The number of average lumbar punctures was decreased to 3.5.

Attention is directed to the ten-year age groups, one to thirty years. Forty-eight cases were treated with a mortality of 23.7 per cent. Included in the fifteen deaths were ten in which death occurred within forty-eight hours after admission. A high mortality for the oldest age group, forty to seventy years, manifested itself as it did in 1935. In the age group forty-one to fifty years, there were five cases with four deaths, and in the age group sixty-one to seventy years, one case and one death.

Tucker reported an epidemic of meningococcus meningitis in Springfield, Ill., and vicinity during 1935. His first sixteen cases were treated intraspinally with antimeningococcic serum with ten deaths or a mortality rate of 62.5 per cent. Subsequently fifty-three cases were treated with antitoxin (Ferry) intravenously and intraspinally with fifteen deaths, or a mortality rate of 28.3 per cent. Complications were surprisingly few in this last group.

Occasionally during 1936 patients were treated by intravenous antitoxin only with excellent results. A five-year-old white male admitted in coma, slow in responding to therapy, received a total of 263,000 units (790 c.c.), a total of fifteen intravenous injections before recovery was complete. A six-month-old infant recovered following three intravenous injections, a total of 60,000 units (180 c.c.).

Hoyne, in 1936, reported a total of ninety-six patients treated exclusively by the intravenous route with a fatality of 15.9 per cent. He also reported nine meningococcic patients treated intravenously without any lumbar punctures and with only one death. He likewise urges massive doses of antitoxin intravenously, the initial dose ranging from 50,000 to 100,000 units. The smaller dose for a child and the larger dose for an adult.

During 1937, to May 1, we treated nineteen patients with intravenous antitoxin only (Ferry). The age groups represented ranged from eight months to forty years. Two deaths occurred under one year despite massive doses of antitoxin, and one death occurred at eleven years. The average mortality for this group was 15.7 per cent. There were fifteen white patients and four colored patients.

TABLE I

INTRAVENOUS ANTITOXIN ONLY

(WHITE AND COLORED) COMBINED DISTRIBUTION FOR 1937

AGE GROUP	CASES	DEATHS	MORTALITY RATE PER CENT
Under 1 Year	2	2	100
1-10	8	0	0
11-20	5	1	20
21-30	3	0	0
31-40	1	0	0
Total	19	3	15.7

Massive intravenous doses were constantly given. The average for each patient was 132,000 units, or 396 c.c. The smallest amount administered to one patient was 30,000 units, or 90 c.c. The largest amount given to one patient was 260,000 units. The initial dose for adults in this small series was at least 50,000 units or 150 c.c. diluted in at least two or three times its volume of 10 per cent glucose. Adrenalin in dosage of 10 minims has been added with each dose of intravenous antitoxin. Mention should be made of a severe sickle-cell anemia in a five-year-old negro male child with an associated meningococcic meningitis. This patient made a complete recovery from his meningitis with 110 c.c., or 36,000 units, of Ferry's antitoxin given intravenously on two successive days.

Table II gives a summary of the ten-year age groups of patients treated with antitoxin (Ferry) from January, 1933, to May 1, 1937. The high mortality under one year of age averages 76.9 per cent and shows little change from a similar group treated with standard meningococcus serum from 1930 to 1932 (77.7 per cent). The three decades on to thirty years include 135 antitoxin-treated cases with an average mortality of 23.8 per cent as compared with 161 serum-treated cases from 1930 to 1932 when the mortality was 42.4 per cent. For the older groups, forty to seventy-five years, the mortality was 68.6 per cent in the antitoxin cases as compared with 79.6 per cent in the serum-treated cases.

TABLE II

ANTITOXIN-TREATED CASES ACCORDING TO 10-YEAR AGE GROUPS (1933 TO 1937)

AGE	CASES	DEATHS	MORTALITY RATE PER CENT
Under 1 yr.	13	10	76.9
1-10	57	14	24.5
11-20	50	11	22.0
21-30	28	7	25.0
31-40	12	6	50.0
41-50	10	9	90.0
51-60	3	2	66.6
61-70	1	1	100.0
71-80	2	1	50.0
Total	176	61	34.6

The average mortality was 34.6 per cent for 176 antitoxin-treated cases between 1933 and 1937. Excluding the 24 deaths within twenty-four hours, a rate of 24.3 per cent and excluding the 8 deaths within forty-eight hours, a rate of 20.1 per cent would have been obtained.

Table III summarizes all cases treated with antitoxin (Ferry) both intraspinally and intravenously for the years 1933, 1934, 1935, and 1936, as well as the small series of nineteen cases treated exclusively by intravenous antitoxin. Conspicuous is the sharp increase in the intravenous dose from an average of 10,000 units in 1933 and

1934 to 27,000 units in 1935 and 53,000 units in 1936. The average intravenous therapy for the nineteen cases in 1937 was 132,000 units. The decrease in the number of intrathecal treatments diminished from an average of 5.1 per cent in 1933 to none in 1937.

TABLE III

ALL ANTITOXIN TREATED CASES

YEAR	CASES	DEATHS	AVERAGE UNITS I.S.	AVERAGE UNITS I.V.	I.S. INJ.	% MORTALITY
1933	14	2	30,000	10,000	5.1	14.2
1934	10	4	30,000	10,000	5.1	40.0
1935	63	29	30,160	27,000	5.0	46.0
1936	70	23	20,000	53,000	3.5	32.8
1937	19	3	0	132,000	0	15.7
Total	176	61			Average	34.6

The complications among these antitoxin-treated cases have been few in number compared with former series of serum-treated cases. Serum reactions have occurred in 40 per cent of all cases. In the small group of nineteen cases treated only with intravenous antitoxin, serum sickness has occurred in 74 per cent of the cases.

A survey of a busy seventeen-year service at the Isolation Hospital recalls the altogether too numerous intrathecal punctures and serum treatments which were administered at intervals of every eight or twelve hours. Unquestionably in cases of sepsis in the past with a low degree of meningitis, we have activated the meningitis by all too frequent lumbar punctures. Lumbar punctures may well serve their purpose for diagnosis and for the relief of intracranial pressure symptoms. Our attention should be directed toward the toxicity of the disease, and we should look upon the meningitis as being secondary to a systemic infection. This attitude might be likened to that assumed now in the treatment of tetanus and diphtheria. Therefore we should concentrate our efforts in terms of how much antitoxin (Ferry) is required for treatment.

SUMMARY

Attention is directed to the increasing incidence and mortality of meningococcus meningitis among certain large cities in the United States over a period of ten years, especially during the last three years. In the United States the average fatality for 1934 and 1935 was 53.2 per cent. Figures are cited showing that Memphis fatality rates from 1925 to 1933 averaged 52.1 per cent.

Tables are shown with various age groups ranging from five months to seventy-five years. The fatality rates for 176 antitoxin-treated (Ferry) patients was 34.6 per cent. For 135 patients ranging in age from one to thirty years, the average was 23.8 per cent.

Figures and tables are cited to demonstrate that with increased massive intravenous doses of antitoxin, a decreased fatality is obtained.

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Treatment of Meningococcic Meningitis With Sulfanilamide

Francis F. Schwentker, M.D.

During 1935 and 1936 an epidemic of meningococcic meningitis in Baltimore caused the admission of over 400 cases to the Syndenham Hospital. In the fall of 1936 sulfanilamide was introduced as a chemotherapeutic agent. Encouraged by good experimental results in animals we administered sulfanilamide to two patients with meningococcic meningitis whose course under serum therapy had been unfavorable. Both patients showed immediate improvement and recovered. Since that time sulfanilamide has been used in the treatment of all patients admitted to the hospital with meningococcic infection.

Method of Treatment.—The drug is usually administered both intraspinally and subcutaneously. To some patients it has been given by mouth. For parenteral injection, 1 per cent solution of the powdered crystalline sulfanilamide (Merck) is prepared in physiologic solution of sodium chloride. This solution is injected intraspinally in amounts varying from 10 c.c. to 30 c.c. and subcutaneously in volumes of 100 to 500 c.c., according to the weight of the patient. Both the intraspinal and subcutaneous injections are repeated every twelve hours until there is definite improvement in the patient's condition and thereafter at twenty-four-hour intervals for a few injections. The treatments are usually discontinued when the cultures of two or three consecutive specimens of spinal fluid have proved sterile.

In order to control the effectiveness of the treatment we have found it advantageous to follow the concentration of sulfanilamide in the blood and spinal fluid. The dosage of the drug is regulated to maintain a concentration of sulfanilamide not less than 5 mg. per 100 c.c. in the spinal fluid and preferably as near 10 mg. per 100 c.c. as possible. These values are given for specimens taken twelve hours after the last injection of sulfanilamide. Because of the rapid absorption and excretion of the drug, the time elapsing between administration of the sulfanilamide and withdrawal of the specimen for analysis must be considered. If spinal fluid is analyzed six hours after intraspinal injection of sulfanilamide, from 15 to 25 mg. per 100 c.c. will be found present. This value exceeds the level in the blood. At twelve hours, however, the spinal fluid value is slightly less than the concentration in the blood.

Results.—Up to the present time 52 patients consecutively admitted with meningococcic infections have been treated with sulfanilamide. In the majority of cases the spinal fluid became sterile following the first injection of the drug, the spinal fluid cell count fell rapidly to normal, the proportion of polymorphonuclear cells decreased progressively, the sugar content increased; and the patient showed rapid recovery. In a few patients several treatments were required to sterilize the spinal fluid; the maximum number has been five, representing two and a half days of treatment.

Of the 52 patients treated with sulfanilamide, eight died. This is a mortality of 15 per cent. Two of these patients were moribund on admission and died three

and seven hours, respectively, after admission. If these cases are excluded there remain 50 cases with 6 deaths, a mortality of 12 per cent. Of 278 consecutive patients treated with antimeningococcus serum in the months immediately preceding the instigation of sulfanilamide therapy, there were 85 deaths, or 30 per cent mortality, compared with 15 per cent for the drug. Excluding cases in which death occurred within twenty-four hours, there were 237 serum-treated patients with 44 deaths, or 19 per cent mortality, compared with 12 per cent mortality with sulfanilamide.

There have been too few patients treated with sulfanilamide to draw any comparisons as far as complications are concerned. Arthritis and transient deafness were observed, but all patients were discharged well.

It is of interest that no report of a case has yet reached our attention in which the sulfanilamide failed to sterilize the spinal fluid promptly. Even in those patients who died, the organism could not be recovered after the first few treatments. These patients had considerable encephalitic involvement and continued moribund throughout their course.

Toxicity.—Certain toxic effects for sulfanilamide have been noted by many observers. Sulphemoglobinemia, hemolytic anemia, acidosis, and moribilliform rash have been described, but only sulphemoglobinemia has occurred in this series of patients. None of these complications is serious if constantly expected and treated appropriately.

Conclusion.—It seems reasonable to conclude that sulfanilamide is as effective in the treatment of meningococcic infection as specific antiserum and has the advantage of freedom from foreign protein properties.

DISCUSSION

DR. E. E. MARTMER (DETROIT, MICH.).—Since commercial serums contain about 50 per cent as much antitoxin as does the commercial antitoxin, why do large doses of serum fail to reduce case fatality rates?

CHAIRMAN HOYNE.—I think serum does reduce case fatality rates when used in large enough doses. Most of the statistics on serum therapy have been based on the use of relatively small doses of serum as compared with the doses of antitoxin now being used.

DR. L. S. FRIEDMAN (CINCINNATI, OHIO).—Do you attempt to test all cases for horse serum sensitivity?

CHAIRMAN HOYNE.—We do not test routinely. We start our serum very slowly and always give adrenalin mixed with it. We do test patients who give a suspicious history.

DR. FRIEDMAN.—What procedure do you follow if a patient is sensitive?

CHAIRMAN HOYNE.—We give the serum by the intramuscular route before intravenous administration. For example, recently we had two patients who relapsed after having had intravenous treatment. One was a serum-treated patient and the other an antitoxin treated patient. An attempt was made to give intravenous therapy again and both had reactions. Antitoxin was then given intramuscularly on three successive days; sterile cultures resulted; and both patients recovered.

DR. A. E. AMICK (CHARLESTON, W. VA.).—What is the minimum dose of antitoxin?

CHAIRMAN HOYNE.—Not less than 60,000 units. This may be all that is needed. In severe cases we usually give 100,000 units or more as the initial dose.

DR. AMICK.—How rapidly is this given?

CHAIRMAN HOYNE.—We begin our intravenous therapy using 10 per cent glucose solution in normal saline containing adrenalin and gradually add the antitoxin to this solution. We start with 10 drops per minute and gradually increase to 60 drops per minute.

DR. H. P. FINE (PERTH AMBOY, N. J.).—Is there any objection to giving the serum faster than 60 drops per minute because of the difficulty of staying in the vein?

CHAIRMAN HOYNE.—I do not think so if no harmful effects manifest themselves. The concentration of substances in the spinal fluid is dependent upon their concentration in the blood stream and the ability of those substances to pass through the barrier between the two. Any foreign substance introduced *directly* into the spinal fluid, as by lumbar puncture, will produce meningitis; this means an increase in the permeability of the meninges. Therefore I feel convinced that patients are much better off if they have nothing intraspinously.

DR. SHAW.—Can you demonstrate antitoxin in the spinal fluid after it has been given intravenously?

CHAIRMAN HOYNE.—Yes, experimental work (by Philip Miller) on mice has shown that antibodies pass from the blood stream into the spinal fluid. Spinal fluid from patients treated with antitoxin intravenously was used in this investigation.

DR. SHAW.—How about the various types of meningococci, do they influence the mortality?

CHAIRMAN HOYNE.—Formerly we paid a great deal of attention to typing the organism. Now very little consideration is given to types and much more to toxic effects.

DR. E. S. PLATOU (MINNEAPOLIS, MINN.).—Have any comparative fatality rates resulting from different methods of treatment during a single outbreak of meningitis been made?

CHAIRMAN HOYNE.—Yes, this was done in Los Angeles and also in Detroit, where the patients were divided into two groups, one receiving serum intravenously and intraspinally and the other receiving the serum intravenously and intracisternally. The groups treated intravenously and intracisternally showed the better results in both instances. However, the group treated intracisternally received larger doses intravenously and this might explain the lower fatality rate although credit was given to the intracisternal method of treatment.

DR. C. H. SMITH (NEW YORK, N. Y.).—There has been an average of 30 to 100 cases per year on the East Side of New York. Under advice of the New York Department of Health, we previously treated cases of meningococcic meningitis with a single daily treatment of serum intraspinally. Intravenous serum was not advised. At present at Bellevue Hospital we treat patients intravenously twice a day for one or two days, and intraspinally twice a day for three or four days (using city or state serum), then switch to one intraspinal treatment a day. If you depend on culture to guide you in stopping or starting treatment, you have to wait too long. Treatment should be determined in this disease by the same methods that one uses in treating a case of appendicitis. In meningococcic meningitis one should be guided by temperature, a daily white blood count, and by the number of cells in the spinal fluid.

DR. AMICK.—How is the early diagnosis of meningitis made without a puncture?

CHAIRMAN HOYNE.—In an epidemic you can be fairly sure of the diagnosis. We depend upon blood cultures, as a rule, to confirm the clinical diagnosis. It is true that there are certain types of hemorrhagic smallpox that are almost impossible to distinguish from meningococcic meningitis. Patients showing petechiae should always have a blood culture. Sometimes the petechia may be pricked by a needle and the organism obtained on smear. If the blood culture is negative, an examination of the spinal fluid is required for a certain diagnosis.

QUESTION.—Do you find a low percentage of negative blood cultures during the first few days?

CHAIRMAN HOYNE.—Seldom do we get a positive blood culture if the patient does not have petechiae.

DR. MARTMER.—What relation do you feel exists between the decline in the outbreak of meningitis in Chicago and the improvement in case fatality?

CHAIRMAN HOYNE.—We are still having a number of cases in Chicago. The severity of the disease does vary during epidemics and also among endemic cases. During 1928-1932 in Detroit, Dr. Gordon stated the cases were severe, and he seemed to attribute that fact to the presence of an epidemic. In 1936 we had 144 cases at the Cook County Hospital with 44 deaths, 20 dying within forty-eight hours of admission. This gave us a very favorable fatality rate. In 1934 and 1935 the fatality rate was also low, but the number of patients was considerably higher than in 1936. It has been my experience that endemic cases of meningococcic meningitis are frequently as severe as those encountered during an epidemic.

DR. SHAW.—Do you think the reverse is true?

CHAIRMAN HOYNE.—Patients with petechiae were regarded by us as having a very bad prognosis when admitted to our hospitals some years ago. Now we feel the opposite is likely to be true unless the patient is suffering from a fulminating type of infection. A patient with petechiae is likely to be diagnosed earlier, and there may be little or no apparent involvement of the meninges. Consequently the chances for recovery are favorable. But even with early treatment the mortality is always high for fulminating cases.

CHAIRMAN HOYNE.—I see Dr. Neal in the room and I am sure all of us would appreciate a few words from her.

DR. JOSEPHINE B. NEAL (NEW YORK, N. Y.).—Infections of meningococcus should be considered meningococcemia with or without meningitis. In New York during the last two or three years we have had meningococcemia with very mild meningitis. These cases respond to intravenous therapy. I would not dare treat a case of meningitis without intraspinous treatment. We use serum intraspinously once a day and only give intravenous serum where there is a septicemia. I have only had a limited experience with sulfanilamide and am using it with serum at the present time. Much of the confusion with methods of therapy is due to the serum's varying in potency. Some serums tested very little better than horse serum during 1926-30, whereas the New York state serum was good. Naturally using such serums would give varying results. We must keep clearly in mind the difference in the septicemic type, which responds to intravenous therapy, and the meningitic type of the disease, which responds to intraspinous therapy.

CHAIRMAN HOYNE.—I am still surprised that Dr. Neal likes to give serum intraspinously.

DR. NEAL.—Your cases were those of the septicemic type with very mild meningitis.

CHAIRMAN HOYNE.—Patients treated intraspinously usually have opisthotonus. Our patients do not have opisthotonus, nor do they develop blocks. We have fewer complications, such as panopthalmitis or pericarditis. Streptococcic meningitis will occasionally follow intraspinous therapy. We do not have that. There is less likelihood of traumatic complications due to injury of intervertebral discs and other spinal tissues as the result of faulty punctures. Our patients are much more comfortable, and there are fewer deaths. Whether the patient is seen on the first day of the disease when there may be meningococcemia with no apparent evidence of meningitis, or whether the patient enters the hospital with meningitis of many days' or weeks' duration and perhaps in a state of extreme opisthotonus, no intraspinal therapy is adopted. During a period of twenty-five years we have had all varieties of meningococcic meningitis on my service at the Cook County hospital. The percentage of severe cases treated without intraspinal therapy during any one of the last few years has been as high as in any one year when intraspinal treatment was practiced.

QUESTION.—How about sequelae?

CHAIRMAN HOYNE.—We have not had a single case of loss of vision or hearing when the patient was treated *before* such complications arose, among our antitoxin patients treated without intraspinal therapy. In fact, we have had several cases with endophthalmitis and impaired hearing clear up under intravenous therapy. However, complications do vary in different years.

DR. B. S. DENZER (NEW YORK, N. Y.).—What is there in common between serum and antitoxin? Do immunologists recognize an antibacterial serum?

DR. SHAW.—I feel that the amount of antitoxin, agglutinins, the opsonic index, and the antileucocidin effect only can be measured in a serum, but farther than that we cannot go. The agglutinin content of antibacterial serum does not parallel the therapeutic effect.

CHAIRMAN HOYNE.—There is very little difference between antibacterial serum and antitoxin from the standpoint of recovery. Since producers of serum have recently altered their methods of manufacture, now there is probably a higher antitoxin content in the antibacterial serum.

In answer to several questions relative to dosage of antitoxin: We have not standardized the optimal dosage of antitoxin. We feel the ideal thing to do would be to give the total dose at one time. A few months ago we had a nurse who developed a headache. The next day she had numerous petechiae and was in deep stupor. Immediately she was given 150,000 units of antitoxin intravenously. No lumbar puncture was done. The next day she received another 150,000 units, and the third day, 100,000 units. Blood cultures were positive during this period. The fourth day a spinal tap grew out organisms. She was given more serum and antitoxin until in all she had received over 2,000 c.c. We frequently repeat the dose on subsequent days to avoid relapse, although cultures of spinal fluid often become negative in thirty-six to forty-eight hours. If one week or more elapses without treatment, and then further treatment is indicated, we often give an intramuscular injection of 10,000 units of antitoxin before resorting to additional intravenous therapy.

DR. SHAW.—We sometimes give 80,000 units during a period of five days.

DR. R. P. ROGERS (GREENWICH, CONN.).—What does the purpuric rash of meningitis look like in a dark negro?

CHAIRMAN HOYNE.—Sometimes the rash is hard to see but may be as obvious as smallpox in the negro. The sore throat in meningitis is very important. One member of a family may be a carrier and another may have a pharyngitis or meningococcemia but no meningitis. I feel that a lumbar puncture in a case of meningococcemia with no meningitis may favor the development of meningitis.

DR. PLATOU.—I have slides showing the results of treatment in two cases of meningococcic meningitis, using fever therapy. The first case was a three-and-one-half-year-old child having meningitis with arthritis. Fever therapy alone was used, and the child recovered. The other case was one of chronic meningitis in which fever therapy alone was used, and recovery followed. I feel that this type of therapy is contraindicated in acute cases but that it is useful in the chronic type or in serum-refractive cases. Certain strains of the organism may be more thermolabile than others.

DR. MARTMER.—How does Dr. Levy explain the failure of improvement in the age groups under one year and over twenty to thirty years?

DR. LEVY.—Our results coincide with other statistics. It is true that the two extremes of life carry the highest mortality.

DR. DENZER.—Is there any objection to combining sulfanilamide and serum?

CHAIRMAN HOYNE.—No, I have used both with good results.

DR. DENZER.—Why not give sulfanilamide intravenously?

DR. SCHWENTKER.—Excretion of sulfanilamide is too rapid and you do not get the concentration in the spinal fluid that one gets following the subcutaneous method of administration. Furthermore, dogs show toxic reactions to the intravenous use of the drug and not to the subcutaneous method. The peak of concentration after oral or subcutaneous administration is reached in about four hours.

DR. LEVY.—Is prontosil in 2.5 per cent solution equivalent to a 1 per cent solution of sulfanilamide?

DR. SCHWENTKER.—One can give prontosil and get the same effect, but it has to be broken down into prontylin, requiring about twelve hours. A 2.5 per cent solution of prontosil is equivalent to about an 0.8 per cent solution of sulfanilamide.

DR. SHAW.—How do you give sulfanilamide? How do you figure dosage?

DR. SCHWENTKER.—The dose of sulfanilamide which we have used runs about as follows: To infants and children under 40 pounds, 2 to 2.4 gm. per day. To children from 40 to 80 pounds, 3 to 3.6 gm. per day. To children weighing over 80 pounds, 4 to 4.8 gm. per day. This is given by mouth or subcutaneously, at four-, six- or eight-hour intervals. In very severe infections we double the dose mentioned. On the first day the dose for twenty-four hours may be given at once. The largest dose which has been given is 5 gm. for an infant, for older children, 7.5 gm., and for adults, 10 gm. One half of the patients treated will become cyanotic, but this can be disregarded.

QUESTION.—What are the toxic effects?

DR. SCHWENTKER.—In addition to the cyanosis, which is due to sulphemoglobinemia and clears upon stopping the drug, we have seen a morbilliform rash appear after two or three days of medication. Acidosis occurs frequently. Transient nausea occurs when the drug is being administered by mouth. Dizziness may occur. Pyrexia may appear and be hard to distinguish from the fever of infection. Hemolytic anemia has been reported. We have never had to interrupt treatment because of toxic effects.

DR. C. L. LAMAR (BIRMINGHAM, ALA.).—Can sulfanilamide be given intraperitoneally in infants?

DR. SCHWENTKER.—Yes, if desired.

DR. LEVY.—If optimal results are obtained by maintaining concentration in the blood at a certain level, can the analysis be made easily?

DR. SCHWENTKER.—Yes, the technic was described by Marshall, E. K., Jr., and his associates: Para-Aminobenzenesulfonamide, J. A. M. A. **108:** 953 (March 20), 1937.

A colorimeter is required, but we do not buffer the solution. The method is about as complicated as a blood sugar determination.

DR. G. B. HUNT (PITTSFIELD, MASS.).—In the use of prontolyn what has been the effect on the white blood count? In the *New England Journal of Medicine*, a case was recently reported of a patient who had an extreme neutropenia and died as a result of the use of the drug.

DR. SCHWENTKER.—All cases of neutropenia which have occurred have not been proved to be caused by the drug. Agranulocytosis often accompanies a streptococcic throat and other infections. I have heard of two patients with agranulocytosis treated with sulfanilamide, and both recovered.

DR. S. A. ANDERSON (RICHMOND, VA.).—You mentioned treating a few cases by subcutaneous medication only. So far as you have gone, does this seem a better method than combining with the intraspinous treatments?

DR. SCHWENTKER.—If it is necessary to keep the spinal fluid content of sulfanilamide high, then this method should be used more.

DR. ROGERS.—Have you found that sulfanilamide-treated cases produce antibodies? In other words, is sulfanilamide actually toxic to the organism, or does it merely check the growth of the organism until antibodies are produced? Is it necessary to continue sulfanilamide for as long as two weeks after the spinal fluid is normal?

DR. SCHWENTKER.—Sulfanilamide checks the growth of the organism. Phagocytosis further aids the sterilization of the spinal fluid. Treatment is continued three or four days after the first sterile culture is obtained.

CHAIRMAN HOYNE.—Perhaps sulfanilamide may supplant eventually all other therapy in the treatment of meningococcic meningitis. Its lower cost is an important factor.

DR. SCHWENTKER.—Dr. Branham has recently published results in mouse protection tests, which show that the protective value in mice of sulfanilamide and of serum was approximately the same. When used in combination, and apparent synergistic action was obtained.

KATHERINE MERRITT
J. LEWIS BLANTON
Recorders.

News and Notes

The following physicians have been certified by the **American Board of Pediatrics** since the last report. All of these licentiates took the examination. At the last three examinations ninety candidates were examined. Of these, sixty-one passed, nineteen failed, and ten were conditioned.

James Marvin Baty, Boston, Mass.
Earl Hayes Baxter, Columbus, Ohio
J. Travis Bennett, El Paso, Tex.
H. Arthur Berson, Boston, Mass.
Alfred DeBard Biggs, Chicago, Ill.
William Carter Black, San Diego, Calif.
Park Southworth Bradshaw, Ann Arbor, Mich.
Burtis B. Breese, Jr., Rochester, N. Y.
Milo B. Brooks, West Los Angeles, Calif.
Robert Peers Buckley, Duluth, Minn.
Leo B. Burgin, Boston, Mass.
Benjamin Watson Carey, Jr., Boston, Mass.
Harry Ray Carson, Phoenix, Ariz.
Creed F. Cherry, Los Angeles, Calif.
Edward J. Denenholz, Chicago, Ill.
Harry F. Dietrich, Beverly Hills, Calif.
George Eisenberg, Chicago, Ill.
Harry L. Faulkner, Chicago, Ill.
Bernard Fein, Newark, N. J.
Henry F. Gallagher, Los Angeles, Calif.
Morris Gleich, New York, N. Y.
Raymond F. Grissom, Oak Park, Ill.
Thomas Lindner Harris, Los Angeles, Calif.
Harry Horwitz, Oakland, Calif.
John P. Hubbard, Boston, Mass.
Samuel Hurwitz, San Francisco, Calif.
Howard M. Jacobs, Chicago, Ill.
John Richard Jimerson, Long Beach, Calif.
Albert Preston Knight, Waverly, N. Y.
George Buchanan Kryder, Glendale, Calif.
Vernon E. Lennarson, Waukegan, Ill.
Vernon William Lippard, New York, N. Y.
Barnett Lipson, Los Angeles, Calif.
Hubert E. Long, Berkeley, Calif.
Benjamin Jacque Malnekoff, Milwaukee, Wis.
Russell W. Mapes, Beverly Hills, Calif.
Chester I. Mead, Bakersfield, Calif.
Kenneth B. McDonough, Madison, Wis.
James Joseph O'Connor, East Chicago, Ind.
Francis T. O'Donnell, Wilkes-Barre, Pa.
Mark F. Osterlin, Traverse City, Mich.
Samuel E. Pasette, Los Angeles, Calif.
Edwin F. Patton, Los Angeles, Calif.
Charles H. Pettet, Los Angeles, Calif.
Leo S. Radwin, Brooklyn, N. Y.
William Bernard Raycraft, Oak Park, Ill.
William Bryant Richards, St. Cloud, Minn.
Maurice L. Ripps, Elizabeth, N. J.
Geneva Shong Rothemund, Springfield, Ohio
Eli Charles Romberg, Boston, Mass.
Edward Lee Russell, Santa Ana, Calif.
Edwin Phillips Russell, Berwyn, Ill.
Ben Shapiro, New York, N. Y.
Albert W. Snoke, Rochester, N. Y.
Benjamin Spock, New York, N. Y.
Vivian Tappan, Tucson, Ariz.
John Orren Vaughn, Santa Monica, Calif.
Josef Warkany, Cincinnati, Ohio
Samuel M. Wishik, Flushing, N. Y.
Ernest Hamilton Watson, Detroit, Mich.
David W. Whaley, Kitchener, Ontario, Canada

Errata

In the October issue of the JOURNAL, on page 604 in the Round Table Discussion on Treatment of Empyema, line 9 should read: "DR. HEEKS.—We have records of several patients with empyema in the Babies Hospital who have recovered with repeated aspiration alone," instead of, "I have not seen a case of empyema recover with repeated aspiration alone."

In the November issue of the JOURNAL, in the article, "Central Nervous System Diseases in the Course of Scarlet Fever," on page 677 Dr. Top's initials were mistakenly given as J. H. and should read F. H.

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